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Abbreviations

ACE  angiotensin-converting enzyme
ADR  adverse drug reaction
AIDS acquired immunodeficiency syndrome
AV  Atrioventricular
BP  British Pharmacopoeia
BSA  body surface area
CNS  central nervous system
CSF  cerebrospinal fluid
DMARD  disease-modifying antirheumatic drug
ECG  Electrocardiogram
EEG  Electroencephalogram
G6PD  glucose 6-phosphate dehydrogenase
GFR  glomerular filtration rate
HIV  human immunodeficiency virus
HRT  hormone replacement therapy
INR  international normalized ratio
MDI  metered dose inhaler
NSAID  nonsteroidal anti-inflammatory drug
spp.  Species
SSRI  selective serotonin reuptake inhibitor
USP  United States Pharmacopeia
The Drug Formulary Committee

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Acknowledgements

The ninth edition of the Belize National Drug Formulary was modeled off the first WHO Model Formulary.

The Ministry of Health would like to acknowledge the contributions of the following persons towards the preparation of the ninth edition of the Belize National Formulary:

- The chairperson and members of the formulary committee
- Medical consultants and specialists within the Ministry of Health and Non-Government organizations in Belize
- British Medical Association and the Royal Pharmaceutical Society of Great Britain for permission to use material from the British National Formulary of which they are joint copyright holders and are not responsible for the accuracy of the transpositions from the original text
- PAHO/WHO
- Management and staff of Matron Robert’s Polyclinic 11 for their assistance and hospitality during the preparation of the document
Preface

The ninth edition of the Belize National Formulary is being reviewed five years after the previous edition of 2002. In 2002 a review of the formulary was conducted with a consultancy by the consultant of the Barbados Drug Service, Ms. Pamela Payne. From that consultancy an essential Drugs list was developed, but there was no manual produced due to administrative difficulties.

This edition of the formulary was conducted under the directorship of the Chief Pharmacist/Technical Advisor of the Ministry of Health Mrs. Sharon Sanchez-Anderson and her competent team of Pharmacists and Doctors: Mr. Anslem Anene, Mrs. Samira Gongora, Mr. Eugene Echegi, Mrs. Dana El-Amin, Ms. Angella Ebuta, Dra. Adelita Ghazy, Mrs. Sharon Sanchez-Anderson along with Dr. Fernando Cuellar and Dr. Jesus Ken), all Belizean Nationals and past Nigerian Technical Aid Corps representatives.

Pharmaceuticals have assumed an increasing important role in the management of many diseases and therefore the rational use of medication provides an efficacious and cost effective means of treating these diseases.

The design and layout of the text has been adopted from the World Health Organization model formulary to produce an updated, more user friendly and attractive quick reference guide. The formulary committee revised submissions by all specialties and eventually agreed on sixty-nine (69) product additions and twelve (12) deletions during a two days stake holder’s workshop held to obtain the final consensus on the list of drugs to be added and deleted.

The drug listed in the formulary corresponds to the health care needs of the vast majority of the population taking into consideration the prevailing economic climate. A selected list of different drug products has an important influence on several key fiscal administrative and quality control requirements of the pharmaceutical logistics system.
With regards to drug procurement, purchasing power is greatly enhanced by the elimination of duplicate and non-essential products. On the clinical side, doctors are assured that the most effective and safe drugs (Drug of Choice) were selected for inclusion. It must be emphasized that the adoption of the formulary is not and arbitrary administrative or economic measure, but a therapeutically oriented tool to increase the availability of essentials drugs. However, in order for a drug formulary to exert its maximum impact on the care and cost of requirement of the health care system, its implementation and use must be mandated by regulation.

I trust, therefore, that my peer and other health care providers will strictly adhere to the drugs listed in this formulary bearing in mind that provision has been made for specially authorized drugs (SAD) in exceptional cases.....

Sharon Sanchez-Anderson (Mrs.)
Chief Pharmacist./Technical Advisor
Ministry of Heath
DRUGS ADDED TO THE 9TH EDITION OF THE FORMULARY MANUAL

DRUGS ADDED TO THE 7TH EDITION OF THE FORMULARY MANUAL
Products Recommended For Addition
PRODUCT, STRENGTH

Sevoflurane, Inhalation bottle
Midazolam, inj, 15mg
Indomethacin, suppository 100mg
Paracetamol, suppository 100mg
Metamizole, inj, 25,000iu, 1g/2ml, 500mg tab
Loratadine, tab 10mg
Valproic acid, 500mg
Clonazepam, 2 mg
Lamotrigine, tab 25 mg
Amoxicillin + clavulanic acid, tab 500mg + 125 mg
Imipenem + cilastatin,
Azithromycin, cap, 500 mg; susp 200mg/5ml
Fluconazole, cap, 200mg, 150 mg, inj 2mg/ml, susp 50mg/5-ml
Griseofulvin, susp, 10mg/ml
Nystatin, loz 100,000 iu, cream/ointment
Ketoconazole, tab, 200mg, cream, shampoo
Amphotericin B, inj, 50 mg/vial
Flucytocine, inj, 2.5 g
Oseltamivir, cap, 75mg; susp 60 mg/5-ml
Abacavir (ABC), oral solution, 100mg (as sulphate)/5ml
Didanosine (ddl), powder for oral solution, 2g/bottle
Ritonavir, caps, 100mg
Iopinavir + ritonavir (LPV/r), susp, 20mg/80mg; 160ml
Tinidazole, tablet, 500mg
Sumatriptan (imigran), tab, 50 mg
Ciclosporin, cap, 25mg, inj, 50mg/ml
Biperidine, tablet, 4mg
Lеводопа + Карбидопа, tab, 250 mg + 25 mg
Losartan (cozaar), tab, 25mg; 50mg
Nimodipine, cap, 30mg
Metoprolol, tan, 50 mg, 100mg, inj 1 mg/ml-5ml amp
Streptokinase, powder for inj, 1.5 million IU/vial
Simvastatin, tab, 10mg, 20mg
Gemfibrozil, tab. 300 mg, 600mg
Niacin, tab, 600mg
Betamethasone, cream or ointment, 0.1% (as valerate)
Salicylic Acid, Solution, 5%
Permethrin, cream 5%; lotion 1%
Ranitidine, oral solution 75mg/5ml
Omeprazole, tab, 20 mg; inj 40mg
Dimenhydrinate, tab, suppository 10mg
Metformin, tab, 850mg
Pyridostigmine, Syrup
Mivacurium, inj, 2 mg/ml 5-ml amp
Chloramphenicol +prednisolone acetate, solution, 2.5 + 5mg/ml
Neomycin/polymixin/hydrocortisone, otic drops, 0.35%/10,000/1%
Ciprofloxacin, otic drops, 0.2%
Oxymetazoline, nasal drops, 0.5%
Ritodrine, inj 10 mg/ml, 5-ml amp
Haloperidol, LA, liquid prep
Quetiapine (seroquill), tab, 50 mg, 100 mg
Ritalin (methylphenidate), tab, 10 mg, 20 mg SR
Beclometasone, inhal(aerosol), 50 mcg/dose (dipropionate)
Montelukast, tab, 10 mg, 20 mg SR
Prednisolone, syrup, 15 mg/5 ml, 60 ml
Salmeterol, inhal(aerosol) LA
Morphine, oral solution 10 mg (hydrochloride or sulphate)/5 ml
Morphine, tab., 10 mg (sulp),
Morphine, 30 mg CR (sulphate)
Hydromorphone, tab., 4 mg, tab, CR 3 mg
Oxycontin, tab., CR, 20 mg, IR 10 mg
Methadone, Powder, 1 mg/ml
Penicillamine, cap., or tab 250 mg
Methylthioninium chloride (methylene bl), inj., 10 mg/ml in 10-ml ampoule
Praziquantel, tab., 150 mg, 600 mg
Clozapine,
PRODUCTS RECOMMENDED FOR DELETION

Lidocaine inj, 1%; topical 2%
Sabutamol inj
Cimetidine 200mg/2ml inj
Naphazoline + Antazoline ophthalmic 0.05% +0.5%
Budesonide aerosol spray inhaler, 200 mcg
Chlopropamide tab, 250 mg
Tolbutamide tab, 500mg
Valproic acid cap, 250 mg, replace with enteric coated tab
SECTION 1

GUIDE TO RATIONAL PRESCRIBING
PRESCRIPTION WRITING

The writing of prescriptions is a vital component of the prescriber’s management of a patient. The written prescription is a means of direct communication from the doctor to the dispensing pharmacist. It is also an important legal document. Careful prescription writing reduces time spent by the pharmacist in contacting the doctor for clarification, improves patient compliance, and reduces life-threatening errors. It is therefore imperative that sound guidelines for prescription writing be established and followed scrupulously.

Legibility is most important. Poor writing leads to many kinds of errors. The patient should be told the name of the drug and asked to commit it to memory.

Many drug names are similar so care must be taken to write them clearly. Abbreviations should not be used. Generic names are preferred unless a specific brand name is required for a special reason. The formulary lists drugs under generic names. Brand names are listed to aid in identification.

The formulation should be convenient and easy to take. Consideration must be given to age, disability, and intelligence of the patient along with the cost of the drug comparing dosage forms (e.g. oral liquids and injections are much more expensive than tablets and capsules).

The doctor’s signature must be written clearly if headed notepaper is not used. The use of pre-signed prescription blanks is discouraged. If used, they must be safeguarded.

There are two general prescription formats:

1. The outpatient prescription, written on a prescription sheet, e.g. a hospital prescription form, a doctor’s headed notepaper, or patient’s personal medical notebook.
   - Patient’s name and full address
   - Patient’s age
   - Date
   - Drug name
   - Dosage strength: e.g. 100mg
   - Dosage form: e.g. suspension, enteric coated tablet, etc.
   - Route of administration
   - Frequency of administration
   - Duration of administration: either indicate the number
of days or the total number of doses to be taken. Do not prescribe PRN, write minimum dose interval

- Particular guidelines: e.g. take with meals
- Repeats: e.g. repeat twice only, or no repeat
- Signature
- Printed name
Rational Prescribing

1. The **inpatient** prescription is written on the patient’s treatment card and included in the hospital notes.

Generally the same structure applies to the prescription written on the treatment card.

Inpatient treatment more often involves the use of narcotic and controlled substances, multiple drug therapies and frequent changes.

**Narcotics and Controlled substances** must be written on the Special Narcotics prescription pads that are recorded in triplicates. The instructions must be written in words (*one fifty milligram tablet to be taken every four hours for ten days, dispense sixty tablets*). Accurate prescription writing and double checking are mandatory. Always specify the dosage, duration and route of administration.

**PRESCRIPTION DISPENSING**

Dispensing is more than just handing the patient an envelope full of tablets. The role of the dispensing Pharmacist is to assure the patient’s compliance to the doctor’s prescribed therapy. Patient compliance can be improved through **proper**
dispensing practices and patient counseling. A properly labelled prescription will remind the patient of the dosage schedule, prevent confusion with other prescriptions or those of other family members, and serve as a record for the patient and doctor. The prescription label should include:

- Patient name and full address
- Date dispensed
- Pharmacist’s initials
- Place of issue (which hospital or health center)
- Prescription number
- Directions for use
- Doctor’s name
- Drug name, strength, quantity and expiration date

SAMPLE PRESCRIPTION LABEL

<table>
<thead>
<tr>
<th>NAME OF PATIENT</th>
<th>N A M E</th>
<th>A N D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDRESS</td>
<td>OF INSTITUTION</td>
<td></td>
</tr>
<tr>
<td>PRESCRIPTION NUMBER</td>
<td>DATE</td>
<td></td>
</tr>
</tbody>
</table>

NAME OF THE DRUG
DOSAGE INSTRUCTIONS

PHARMACIST’S INITIAL

Tropical conditions found in the Belize necessitate that extra attention is given to proper packaging of the prescriptions. The use of paper envelopes is not recommended as it allows exposure to air and moisture, promoting rapid degradation and loss of potency. Specific examples of products that are especially vulnerable to moisture are aspirin and sugar coated tablets. Glyceryl trinitrate must ideally be dispensed in the original container or an amber vial with a tight seal or the tablets will lose their potency in a matter of days.

Pharmacists must make every effort to dispense the complete amount prescribed by the doctor. “Short dosing” a patient (e.g. dispensing 100ml of suspension when 120ml is prescribed) does not save money. Incomplete therapy will likely cause a relapse or treatment failure thereby necessitating another
Rational Prescribing

prescription. Use purified bottle water or boiled (and cooled) water to mix suspensions. Suspensions should NEVER be dispensed without being reconstituted by the pharmacist.

The Pharmacist should counsel the patients regarding prescriptions to improve their understanding of why they are taking the drug, how to take it and what effects it may have. The drug monographs in SECTION II of this manual include precautions, adverse reactions and other information which may be communicated to the patient. The pharmacist should select the most important points and inform the patient. These may include:

- Timing of dosage: e.g. at bedtime; with meals; etc.
- Significant or common adverse reactions: e.g. drowsiness; dizziness; blurred vision
- Special instructions: e.g. “Report to doctor if rash occurs”; or, “Do not stop taking this medication unless you inform your doctor”
- Patient counseling also includes asking the patient questions to test his/her understanding (e.g. “How many times a day do you take this drug?”) and detect potential problems (e.g. “What other drugs are you taking?”; “Do you have any drug allergies?”).

VARIATION IN DOSE RESPONSE

Successful drug therapy depends not only on the choice of the most appropriate drug but also on the best dosage regimen for each individual patient. Administering the same dose to different patients yields a wide variation in responses. Prescribing the “usual” adult dose may not result in treatment success for a variety of reasons.

- **Patient non-compliance:** more problematic in patients with asymptomatic or chronic illnesses (e.g. hypertension, diabetes), and in epilepsy
- **Age, sex, and weight differences:** especially the very young or very old
- **Disease states:** Hepatic and renal impairment (particularly), pulmonary or cardiac disease, and obesity may alter distribution, metabolism, or elimination of drugs
- **Diet and nutritional status:** Malnutrition delays drug metabolism. Dairy foods lower tetracycline bioavailability
- **Therapeutic/Toxic ratio:** Drugs with narrow therapeutic indices such as digoxin, gentamicin, theophylline, and phenytoin require special attention to dosage regimens
- **Drug interactions:** Aspirin displaces warfarin from RBC’s
Drug formulation: Time-released preparations cause more variation in response.

Route of Administration: Oral forms less predictable than IV, rectal absorption erratic except for metronidazole.

Environmental: Smoking decreases theophylline and imipramine blood levels.

In summary, prescribers should consider these factors when prescribing for each patient or assessing patient response to drug treatment.

Prescribing for Children

Children, and especially neonates, require careful consideration for dosing of drugs. There is a high degree of variation in response to drugs administered to infants and children. This is especially true during the first month of life. The individual drug monographs in this manual contain guidelines for dosing children of 1 year or older based on body weight. It must be emphasized that these are estimates only and that they must be verified by clinical experience. If no dosage is stated in the monograph, this indicates that either no dosage adjustment is needed (e.g. topical preparations) or that the drug is not recommended for use in children (e.g. tetracycline).

To estimate dosages of drugs not contained in this formulary the following chart may be used as a rough guideline for estimating dosage.

<table>
<thead>
<tr>
<th>AGE</th>
<th>WEIGHT (KG)</th>
<th>% OF ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOSE</td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>less than 12</td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>3.4</td>
<td>12</td>
</tr>
<tr>
<td>3 weeks</td>
<td>4.0</td>
<td>14</td>
</tr>
<tr>
<td>2 months</td>
<td>4.5</td>
<td>15</td>
</tr>
<tr>
<td>4 months</td>
<td>6.5</td>
<td>1</td>
</tr>
<tr>
<td>6 months</td>
<td>7.4</td>
<td>21</td>
</tr>
<tr>
<td>9 months</td>
<td>9.1</td>
<td>24</td>
</tr>
<tr>
<td>1 year</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>3 years</td>
<td>14-15</td>
<td>33-35</td>
</tr>
<tr>
<td>6 years</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>9 years</td>
<td>29</td>
<td>61</td>
</tr>
<tr>
<td>12 years</td>
<td>40</td>
<td>75</td>
</tr>
</tbody>
</table>
Specific drugs that appear to have a greater or more prolonged effect in infants than in adults are: indomethacin, aspirin, paracetamol, diazepam, phenobarbital and phenytoin. Later in childhood these anticonvulsants and theophylline are metabolized more rapidly than in adults.

In prescribing for children, one should consider the various formulations available and their relative costs. Oral syrups or suspensions are accepted more readily by children but are much more expensive. Note the following cost comparison for a course of cloxacillin therapy based on 2007 prices.

CLOXACILLIN 250MG CAP 4/DAY X 5 DAYS: BZ$0.80
CLOXACILLIN 250MG SUSP 4/DAY X 5 DAYS: BZ$4.64

Generally, children over 6 years old can be persuaded to take solid dosage forms. If they have difficulty, tablets may be crushed or capsules may be placed inside a small piece of banana or other types of food before swallowing.

**PREScribing FOR THE ELDERLY**

Special consideration is required when determining dosage regimens for the elderly. Although 60 is often considered the age when the deterioration of organ systems affects the patients response to drugs, **there is a high degree of variation between individual patients.** Generally, drug dosages are much lower in the aged because of reduced body mass, metabolizing capacity and renal function. Drugs that are commonly implicated for causing the majority of adverse drug reactions in elderly patients are: digoxin, hypnotics, psychotropics, aspirin and oral hypoglycemic agents.

A few general principles should be considered when prescribing for the elderly:

1. **Determine what other drugs the patient is taking,** including non-prescribed drugs.
2. Request that the patients bring in their tablets and bottles with them to the clinic. The patient should take as few medications as possible.
3. **Determine if the patient is capable of understanding** how to take the medications prescribed. If not, a third party will be needed.
4. **The dosage schedule should be as clear and simple as possible.** The prescriptions must be clearly marked with instructions for use. Do not write, “Take as directed or when necessary”.
5. **Monitor the patient closely** for adverse reactions, compliance and therapeutic response.
6. **Consider the patients’ disease states** and how they will affect the way the drugs will respond in the
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body. How will each drug be affected by changes in hepatic, renal, and cardiac function?

PRESCRIBING IN HEPATIC DISEASE

The liver affects the response to many drugs in a variety of ways. The liver biotransforms some drugs into inactive metabolites that are readily excreted in the urine. A few drugs are biotransformed into active metabolites (e.g. prednisone into prednisolone). Biotransformation is a function of hepatic blood flow, therefore, patients with impaired hepatic function may have an increased or prolonged response to certain drugs. This is common in the elderly. Liver enzyme tests are not a good indication of the liver’s ability to biotransform drugs. Prothrombin time and serum albumin are better indicators. Patients with hepatic impairment must receive reduced doses of drugs in which elimination is dependent on hepatic function. Examples: lignocaine, beta-blockers, aminophylline, ergotamine, phenytoin, metronidazole, rifampicin and sulphonylureas.

Fluid overload is a particular problem in some patients with hepatic disease. Drugs with a high sodium content or those that cause sodium retention should be avoided. Examples: Antacids, prednisolone, ampicillin inj. and carbenicillin inj. Drugs that cause hypokalemia may precipitate coma. Examples: Non-potassium sparing diuretics, antineoplastics. Drugs that impair cerebral functions may contribute to hepatic encephalopathy. Examples: sedatives, hypnotics, anxiolytics, narcotic analgesics, antihistamines and phenothiazines. Certain drugs have been identified as causing hepatotoxicity. When these drugs are given to patients with impaired hepatic function there is an increased risk of hepatotoxicity. Examples: methyldo pa, chlorpromazine, paracetamol, erythromycin estolate, isoniazid, pyrazinamide, rifampicin and tetracycline injection.

The individual drug monographs in this manual identify those drugs which are contraindicated or for which precaution must be taken in their use for patients with impaired hepatic functions.

PRESCRIBING IN RENAL DISEASE

Renal impairment increases the risk of drug toxicity. Drugs dependent on renal function for their elimination will have a prolonged half-life and therefore a potential for toxic accumulation in patients with renal impairment. Practitioners must understand the relationship between renal function and drug accumulation so they can make appropriate drug dosage adjustments when treating patients with impaired renal function. The renal clearance of drugs which are dependent upon the

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kidneys for elimination parallels the glomerular filtration rate (GFR). If the GFR is known, adjustments can be made in drug therapy. The relevant drug monographs in this manual contain specific guidelines for dosage adjustment. These can only be applied if the practitioner can estimate the GFR. The GFR can be determined by measuring urine output or requesting laboratory tests for serum creatinine and extrapolating this value to a predicted GFR. There is no universally reliable method for making this extrapolation. The following equation, which uses age and serum creatinine as variable, can be used to calculate the GFR (creatinine clearance).

\[
98 - [0.8 \times (\text{AGE} - 20)]
\]

For males, \(\text{GFR (Cr. Cl.)} = \frac{98 - [0.8 \times (\text{AGE} - 20)]}{\text{SERUM CREATININE}}\)

(For females, multiply result by 0.9)

EXAMPLES OF SERUM CREATININE VS. GFR, AT 3 AGE LEVELS

<table>
<thead>
<tr>
<th>DEGREE OF IMPAIRMENT</th>
<th>GFR (CR.CL.)</th>
<th>SERUM (MG/100ML)</th>
<th>CREATININE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>20-50ML/MIN</td>
<td>1.9-4.8</td>
<td>1.5-3.9</td>
</tr>
<tr>
<td>MODERATE</td>
<td>10-20ML/MIN</td>
<td>4.9-9.7</td>
<td>4.0-7.7</td>
</tr>
<tr>
<td>SEVERE</td>
<td>&lt; 10ML/MIN</td>
<td>&gt; 9.7</td>
<td>&gt; 7.7</td>
</tr>
</tbody>
</table>
PRESCRIBING DURING PREGNANCY

Teratogenic effects are dose and time related and the time of greatest risk is during the first three months of gestation. Teratogenic effects are usually thought of as anatomical malformations but evidence has indicated that intellectual, social and functional development may also be affected. Administration of drugs during the 2nd and 3rd trimester may also cause teratogenicity, growth retardation, drug dependence, or other unwanted effects. Drug administration near term should be undertaken carefully as the infant at birth will not yet have developed its own metabolic processes, and drug levels will be prolonged.

The approach to treatment of the pregnant patient is to weigh the seriousness of the pregnant woman’s condition against the risk of harmful effects to the fetus, considering the teratogenicity of the therapeutic agent. Information on the teratogenicity and adverse fetal effects of drugs is not readily available in medical/pharmaceutical texts and when information is found, the guidelines are not definitive. The monographs in this manual inform the prescriber of the relative risk of harmful effects of the fetus using the following terminology, in increasing order of risk to the fetus.

**“No evidence of adverse fetal effects”:** Studies have been conducted and no clear teratogenicity has been found.

**“Potential fetal risk”:** Teratogenicity has been demonstrated in animals but not in humans, or there is a theoretical risk in humans but it has been not proven.

**“High risk to fetus”:** Teratogenicity has been proven and the drug should only be used if the seriousness of the pregnant mother’s condition outweighs the potential risk to the fetus.

**“Do not use”:** Teratogenicity has been proven. There is no clinical situation that justifies the use of this drug in pregnant mothers.

In many cases no studies have been made, the monograph indicates “no data available”, and the practitioner must use clinical judgment.

PRESCRIBING DURING LACTATION

Prescribing to mothers during breastfeeding rarely results in toxicity to the infants, although drugs that are excreted in the breast milk in significant levels must be considered to have the same pharmacological effect upon the infant as they do upon the mother (e.g. hypnotics cause drowsiness). Other considerations:

* Neonates and preterm infants have not developed excretory mechanisms and therefore may accumulate the drugs obtained from mother’s milk.

* Antibiotics may cause modification of gastrointestinal
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flora and produce diarrhea, candidiasis or thrush.

* Allergenic drugs may sensitize the infant or cause allergic reactions.

* Drug exposure to the infant may be minimized by scheduling the mother’s dose just before nursing.

The drug monographs within this manual contain information regarding drug therapy during lactation. In many cases there is no information available and the prescriber must use clinical judgment considering the risk/benefit ratio. The information reported in the monographs is usually categorized in the following order of increased risk to the infant:

1) “Not excreted in breast milk”
2) “No evidence of adverse effects to the infant”
3) “Potential risk to the infant”
4) “Avoid drug use or discontinue breastfeeding”

**DRUGS THAT MAY DISCOLOUR FAECES**

**BLACK**
Acetazolamide
Aluminum Hydro xide
Aminophylline
Amphetamine
Amphotericin B
Chlorpropamide
Prednisolone
Digoxin
Ferrous Salts
Hydralazine
Hydrocortisone
Methotrexate
Potassium Salts
Sulphonamides
Tetracycline
Theophylline
Triamcinolone
Warfarin
Corticosteroids

**BLUE**
Chloramphenicol

**GREEN**
Indomethacin

**PINK/RED**
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Anticoagulants
Aspirin-like drugs
Barium
Heparin

**ORANGE/RED***
Rifampicin
Clofazimine

**YELLOW**
Senna
Antibiotics (Oral)
Barium

**BLACK/WHITE SPECKLING**
Aluminum hydroxide

*These colours may indicate intestinal bleeding

**DRUGS THAT MAY DISCOLOUR URINE**

**BLACK/BROWN**
Ferrous Salts
Metronidazole
Nitrofurantoin
Senna

**ORANGE/YELLOW**
Heparin
Rifampicin
Warfarin

**BLUE/GREEN**
Amitriptylline
Indomethacin
Deferoxamine

**RED**
Phenytoin
Senna

**DRUG INDUCED SEXUAL DYSFUNCTION**

**Alcohol**
With increased doses, sexual response is impaired, resulting in failure of erection and reduced vaginal vasodilation and delayed orgasm in females.

**Anticonvulsants**
Reduced male sexual activity due to low testosterone levels.

**Antihypertensives**
Impotence, failure of erection, reduced Libido (except ACE inhibitors, calcium channel blockers)

**Antipsychotics (especially thioridazine)**
Ejaculatory impairment (including retrograde ejaculation and impotence), difficulty in getting erection and delayed ejaculation.

**Marijuana**
Large doses may cause decreased libido and inability of males to perform sexually.

**Spironolactone**
Gynecomastia in males. Large doses commonly cause breast enlargement and menstrual irregularities in females.

**DRUGS SUSCEPTABLE TO RAPID DETERIORATION UPON EXPIRATION**

- Glyceryl Trinitrate Tab
- Epinephrine (adrenaline) Inj
- Tetracycline Cap
- Vincristine Inj
- Ergometrine Inj
- Aspirin Tab
- Phenothiazines
- Diazepam Inj

**DRUG ADMINISTRATION AND FOOD**

Drugs to be taken on an empty stomach - with a full glass of water (1 hour before, or 2 hours after meals)
- cephalexin
- cloxacillin
- erythromycin
- levothyroxine
- tetracycline

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Acetaminophen

**Drugs to be taken 15-30 minutes before meals** - with full glass of water
- Captopril
- Metoclopramide
- Propranolol

**Drugs to be taken preferably on an empty stomach for better absorption but may be taken with food if gastric upset occurs**
- Cephradine
- Ferrous fumarate
- Ferrous sulfate
- Isoniazid
- Rifampicin
- Theophylline
- Acetylsalicylic acid
- Allopurinol
- Ascorbic acid
- Ketoconazole
- Carbamazepine
- Calcium Carbonate
- Chlorpropamid
- Cimetidine
- Doxycycline
- Glibenclamide
- Ibuprofen
- Indomethacin
- Triamterene
- Levodopa
- Metformin
- Metronidazole
- Nitrofurantoin
- Potassium Salts
- Quinidine
- Reserpine

**Drugs that may be given without regard to meals**
- Amoxicillin
- Enalapril
- Erythromycin ethylsuccinate
- Ethambutol
- Lisinopril
- Multivitamins
- Nadolol
- Ranitidine
- Trihexyphenidyl

**EMERGENCY TREATMENT OF POISONING**
TREATMENT OF POISONING

POISONING
In known or suspected poisoning:
1. Assure adequate airway and cardiac support (cardiopulmonary resuscitation).
2. Determine the type of exposure and begin First Aid as follows:

INGESTED POISON:
If poison is not corrosive (acid or alkali) or a petroleum product, and patient is not convulsing, drowsy or comatose
1) Induce emesis with 10-30ml of syrup of ipecac (Child, 6 months - 2 years: 10ml; Older Child: 15ml; Adult: 30ml) and 1/2 glass water. If no or inadequate response within 30 minutes, repeat dose of ipecac and/or proceed to gastric lavage (ipecac is preferable in children - salt solutions are dangerous).
2) Administer activated charcoal slurry by stomach tube (#22 gauge). Lavage with 100-300ml aliquots of warm water or 0.45% (0.5N) saline solution until 3 liters of clear liquid is returned, or with aliquots of activated charcoal if available (100gm/liter) and leave 25-50gm in water in stomach. Charcoal is ineffective against ferrous sulfate, most metallic compounds, mineral acids, alkalis, methanol and DDT. It is most effective against antidepressants, phenobarbitone and phenytoin.

INHALED POISONS:
1) Bring victim to fresh air
2) Remove any airway obstruction
3) Administer oxygen

SKIN CONTAMINATION:
1) Avoid contamination of person administering first aid
2) Drench skin with water (if large portion is contaminated, use of a shower is preferred)
3) Continue drenching skin while removing clothing
4) Cleanse skin with soap and water
5) Do not use chemical antidotes

EYE CONTAMINATION:
1) Hold eyelids apart and flush eye with water for 15 minutes
2) Do not use chemical antidotes

SNAKE BITE:

1) Immobilize the patient and bitten area in a horizontal position
2) Wash the bitten area gently
3) Do not allow the patient to walk, run, drink alcohol or caffeinated beverages
4) Apply constricting bands just proximal and distal to the bite, tight enough to stop lymph drainage but not arteries and veins. As swelling progresses move bands
5) Do not incise through the fang marks
6) Transport the patient to a medical facility where supportive treatment and antiserum can be administered.

COMMON POISONINGS AND TREATMENT GUIDELINES

POISONOUS AGENT
Amphetamines & CNS Stimulants

PRESENTATION
Initially overactive, paranoia, hallucinations; later exhaustion, convulsions, hyperthermia and coma
Chlorpromazine or beta-blocker; sponging, anti-convulsants, and respiratory support

TREATMENT ALTERNATIVES
Chlorpromazine or beta-blocker; sponging, anti-convulsants, and respiratory support

POISONOUS AGENT
Aspirin and salicylates

PRESENTATION
Hyperventilation, tinnitus, vasodilation, sweating

TREATMENT ALTERNATIVES
Gastric aspiration & lavage (up to 24 hours after ingestion of more than 10 tablets); correction of acid-base and electrolyte disturbances; forced alkaline diuresis if plasma salicylate > 50mg/dl in adults, or > 35mg/dl in children

POISONOUS AGENT
Iron Salts

PRESENTATION
Nausea, vomiting, diarrhea, rectal bleeding; hypotension, hepatocellular necrosis and coma may occur

TREATMENT ALTERNATIVES
Induce emesis (ipecac), gastric lavage with desferrioxamine mesylate (sec. 64:00) 2gm in 1 litre
water, leave 10gm in 50ml water in stomach.

**POISONOUS AGENT**
**Morphine & Narcotic Analgesic**

**PRESENTATION**
Pinpoint pupils, respiratory depression, coma

**TREATMENT ALTERNATIVES**
Naloxone (sec. 28:10)

**POISONOUS AGENT**
**Organophosphate**

**PRESENTATION**
Anxiety and restlessness, hypersalivation, miosis, nausea, bradycardia, sweating, abdominal colic, muscle weakness, convulsion

**TREATMENT ALTERNATIVES**
Gastric lavage (if ingested), maintain ventilation and oxygen, atropine (for muscarinic effects, repeat every 20-30 minutes), pralidoxime mesylate (sec. 64:00) in severe cases.

**POISONOUS AGENT**
**Paracetamol**

**PRESENTATION**
Initially nausea, and vomiting, later severe hepatic and renal necrosis at 3-4 days

**TREATMENT ALTERNATIVES**
Induce emesis (ipecac); acetylcysteine (sec. 64:00) or methione within 24 hours of ingestion if 15 tablets or more suspected.

**POISONOUS AGENT**
**Paraquat (grammoxoneR)**

**PRESENTATION**
Initially vomiting and oro-pharyngeal ulceration; renal failure, dyspnea with pulmonary fibrosis several days later.

**TREATMENT ALTERNATIVES**
Fuller’s earth (sec. 64:00) administration and lavage leaving 100ml of 30gm fuller’s earth + 5gm
magnesium sulphate in the stomach.

**POISONOUS AGENT**

**Barbiturates and sedatives**

**PRESENTATION**
Drowsiness, hypotension, hypothermia, respiratory depression, coma

**TREATMENT ALTERNATIVES**
supportive measures, activated charcoal; naloxone to rule out opiates if suspected. Forced alkaline diuresis for severe Phenobarb poisoning only.

**POISONOUS AGENT**

**Petroleum Distillates**

**PRESENTATION**
Initially vomiting, pulmonary irritation; later pulmonary edema, bronchial pneumonia.

**TREATMENT ALTERNATIVES**
Gastric lavage rarely indicated because of the risks if they enter the lung.

**POISONOUS AGENT**

**Phenothiazines**

**PRESENTATION**
Drowsiness, hypotension, hypothermia, ventricular arrhythmias, extrapyramidal symptoms, coma.

**TREATMENT ALTERNATIVES**
Gastric lavage, benztropine (section 12:08) for extrapyramidal symptoms; phenytoin for arrhythmias and convulsions.

**POISONOUS AGENT**

**Theophylline & related**

**PRESENTATION**
Dilated pupils, vomiting, agitation, tachycardia, supraventricular arrhythmia, profound hypokalemia, convulsions, hypotension

**TREATMENT ALTERNATIVES**
Induce emesis & gastric lavage, KCL, diazepam (for convulsions); propranolol (for hypotension and
tachyarrhythmias).

**POISONOUS AGENT**

**Tricyclic antidepressants and related**

**PRESENTATION**

Dilated pupils, hypotension, hypothermia, hyperreflexia, respiratory depression, cardiac arrhythmias and conduction defects, hallucinations, and convulsions.

**TREATMENT ALTERNATIVES**

Gastric lavage and activated charcoal; IV fluids, diazepam (for convulsions), phenytoin (for arrhythmias - monitor heart-beat).
CRITERIA FOR DRUG SELECTION

- Select drugs with demonstrated efficacy and acceptable risk as determined by double-blind clinical studies.
- Avoid unnecessary duplication of drug products or multiple dosage forms, or strengths (scored tablets of certain drugs can be easily broken when precise dosing is not critical, e.g. Diazepam 5mg scored tablets can be broken into two (2) halves to provide 2.5mg tablets).
- Include new products only if clearly clinically superior and/or more cost-effective.
- Add combination products only if they provide real benefit over individual components in terms of efficacy, cost or improved compliance and allow dosage adjustments for the vast majority of patients.
- Select clear drugs of choice for diseases prevalent in the health care environment.
- Include Specially Authorized Drugs (SAD) in exceptional cases for a unique sub-group of patients by medical specialists.

The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

When the strength of a drug is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word “as”.

The square box symbol (Q) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the
lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.”

Drugs are listed in alphabetical order, within sections.

1. **ANAESTHETICS**

1.1 General anaesthetics and oxygen

- **Isoflurane**
  Inhalation, Bottle SAD
- **halothane**
  Inhalation, 0.01%: *Only limited quantity needed*
- **ketamine**
  injection, 50 mg (as hydrochloride)/ml in 10-ml vial
- **nitrous oxide**
  inhalation
- **oxygen**
  inhalation (medicinal gas)
- **thiopental**
  powder for injection, 1.0 g (sodium salt) in ampoule
- **Propofol**
  Injection, 10mg/ml x10ml amp
- **Choral hydrate**
  100 mg/ml
- **sevoﬂurane**
  Inhalation, bottle

1.2 Local anaesthetics

- **bupivacaine**
  injection, 0.5% (hydrochloride) in vial x 20ml injection for spinal anaesthesia, 0.5% (hydrochloride) in 20-ml ampoule to be mixed with 7.5% glucose solution
- **lidocaine**
  injection, 2% (hydrochloride) in vial (plain)
  injection, 2% (hydrochloride) in vial (w/preservative)
  injection for spinal anaesthesia, 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution
  topical forms, 5% (hydrochloride) spray, 100mg
  injection, 4% Cardiac, 2-ml
- **lidocaine + epinephrine (adrenaline)**
  injection 1%, 2% (hydrochloride)+ epinephrine 1:200 000 in vial; dental cartridge 2% (hydrochloride) + epinephrine 1:80 000
1.3 Preoperative medication and sedation for short-term procedures

**Ephedrine**
injection, 30 mg (hydrochloride)/ml in 1-ml ampoule (For use in spinal anaesthesia during delivery, to prevent hypotension)

2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)

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

**Acetylsalicylic acid**
tablet, 81, 300 mg;

**Ibuprofen**
tablet, 200 mg, 400 mg, syrup, 200mg/ml or 100mg/5ml

**Paracetamol** *
tablet, 500 mg; suppository, 100 mg; syrup, 120 mg/5ml
* not recommended for anti-inflammatory use due to lack of proven benefit to that effect

**Naprosen (Naproxen)**
tablet, 250mg, 500mg

**Diclofenac**
Injection im/iv, 25mg/ml/3ml, tablet 50mg

**Indomethacin**
tablet, 25mg, suppository 100 mg

**Metamizole**

2.2 Opioid analgesics

**codeine**
tablet, 30 mg (phosphate)

**acetaminophen/codeine**
Tablet, 300mg/30mg

**morphine**
Injection, 10 mg in 1-ml ampoule (sulfate or hydrochloride); oral solution, 10 mg (hydrochloride or sulphate)/5 ml; tablet, 10 mg (sulfate), tablet CR 30mg(sulphate)

**hydromorphine**
tablet, 4mg, tablet CR 3mg ,

**Oxycontin(oxycodeone)**
tablet Cr, 20mg, IR 10mg

**methadone**
Powder,1mg/ml

**pethidine**
Injection, 50mg/ml,100mg/ml tablet,50mg

**Fentanyl**
Injection as the citrate,50mcg/ml/2ml

2.3 Medicines used to treat gout

**allopurinol**
tablet, 100 mg,300mg

2.4 Disease modifying agents used in rheumatoid disorders (DMARDs)

*All the drugs listed are already on the current formulary except penicillamine*

**chloroquine**
tablet, 100 mg, 150 mg (as phosphate or sulfate)

**azathioprine**
tablet, 50 mg

**methotrexate**
tablet, 2.5 mg (as sodium salt)

**penicillamine**
capsule or tablet, 250 mg

**sulfasalazine**
tablet, 500 mg

3. **ANTIALLERGICS/ANTIHISTAMINE AND MEDICINES USED IN ANAPHYLAXIS**
3. Antiallergics/Antihistamine and Medicines used in Anaphylaxis

**chlorpheniramine**
tablet, 4 mg (hydrogen maleate); injection, 10 mg (hydrogen maleate) in 1-ml ampoule, syrup, 2 mg/5 ml x 100 ml

**promethazine hcl injection**
Injection, 25 mg/ml x 2 ml, tablets, 25 mg

**ketotifen**
syrup, 1 mg/5 ml x 150 ml, tablet, 1 mg

**loratadine**
tablet, 10 mg

**dexamethasone**
injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule

**epinephrine** (adrenaline)
injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule

**Hydrocortisone**
powder for injection, 100 mg (as sodium succinate) in vial

prednisolone tablet, 5 mg, 25 mg* there is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.

**Methylprednisolone** (sod. Succ) 500 mg; 2 ml inj

**Dobutamine**
inj, 25 mg/ml; 10 ml

**Dopamine**
inj, 40 mg/ml; 5 ml

4.1 Non-specific

**Antidote**
charcoal, activated Tablet, 300 mg

4.2 Specific

**Acetylcysteine**
injection, 200 mg/ml in 10-ml ampoule, solution, 20%

**Atropine**
injection, 1 mg (sulfate) in 1-ml ampoule

**calcium gluconate**
injection, 100 mg/ml in 10-ml ampoule * the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

**deferoxamine**
powder for injection, 500 mg (mesilate) in vial

**methylthioninium chloride** (methylene blue)
injection, 10 mg/ml in 10-ml ampoule

**naloxone**
injection, 400 micrograms (hydrochloride) in 1-ml
ampoule
flumazenil
Injection 100 micrograms /ml
penicillamine
capsule or tablet, 250 mg

5. **ANTICONVULSANTS/ ANTIEPILEPTICS**

carbamazepine
scored tablet, 200 mg
diazepam
injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
magnesium sulfate*
injection, 500 mg/ml in 2-ml ampoule; 500mg/ml in 10-ml ampoule* for use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
phenobarbital
tablet, 30mg, 60mg, injection, 200 mg/ml; elixir, 50 mg/5ml
phenytoin
capsule or tablet, 100 mg (sodium salt);
injection, 50 mg/ml in 5-ml vial (sodium salt), syrup, 125mg/5ml
valproic acid
Capsule, 250 mg, 500 mg or enteric coated tablet, 200mg, injection, 100mg/ml x5ml iv
clonazepam *
tablet, 1mg
ethusuximide
Tablet, 250mg
lamotrigine
tablet, 25mg SAD/MONITOR

6. **ANTI-INFECTIVE MEDICINES**

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

**Albendazole**
chewable tablet, 200 mg, suspension 20mg/ml/20ml
**niclosamide** *
chewable tablet, 500 mg* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

6.2 Antibacterials

6.2.1 Beta Lactam medicines

Amoxicillin
capsule or tablet, 250 mg, 500 mg (anhydrous); powder for oral suspension, 125 mg (anhydrous)/5 ml, 250mg/5ml

amoxicillin + clavulanic acid
tablet, 500 mg + 125 mg, suspension, 125mg + 31.25 mg, suspension, /5ml

Ampicillin
powder for injection, 500 mg, or 1 g (as sodium salt) in vial

Amikacin
Injection, 500mg, 100mg,

benzathine benzylpenicillin
powder for injection, 1.44 g benzylpenicillin (=2.4 million IU) in 5-ml vial,

Benzylicillin
powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (sodium or potassium salt) in vial

cloxacillin
capsule, 250 mg, 500mg, (as sodium salt); powder for oral solution, 125 mg (as sodium salt)/5 ml; powder for injection, 500 mg (as sodium salt) in vial

Phenoxymethylpenicillin (Pen V)
tablet, 250 mg (as potassium salt); powder for oral suspension, 250 mg (as potassium salt)/5 ml

procaine benzylpenicillin
powder for injection, 1 g (=1 million IU), 4g (=4 million IU) in vial

Ceftazidime
powder for injection, 500 mg (as pentahydrate) in vial

ceftriaxone
powder for injection, 500 mg or 1 G (as sodium salt) in vial

cefuroxime
Powder for injection, 750mg, suspension 125mg/5ml

cefotaxime
Powder for injection, 500mg,

cefalexin tablet, 250mg, 500mg, suspension, 125mg/ml, 250mg/ml

imipenem * + cilastatin *
powder for injection 250 mg (as monohydrate) + 250 mg (as sodium salt), 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial SAD

6.2.2 Other antibacterials

azithromycin *
capsule, 250 mg or 500 mg; suspension 200 mg/5 ml (AVIAN INFLUENZA) SAD/SPECIALIST PRESCRIPTION
chloramphenicol
capsule, 250 mg; oral suspension, 125 mg (as palmitate) /5 ml; powder for injection, 1 g (sodium succinate) in vial; oily suspension for injection 0.5 g (as sodium succinate)/ml in 2-ml ampoule
ciprofloxacin *
tablet 250 mg (as hydrochloride), 500mg, injection, 400mg, 200mg/ml
doxycycline *
capsule or tablet, 100 mg (hydrochloride)
Vancomycin
Inj 500 mg (vancomycin as the hydrochloride)
erythromycin
capsule or tablet, 250 mg (as stearate or ethyl succinate); powder for oral suspension, 125 mg (as stearate or ethyl succinate);
gentamicin *
injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial* final selection depends on indication for use
metronidazole
tablet, 250mg; injection, 500 mg in 100-ml vial; vaginal pessary, 500 mg; oral suspension, 200 mg (as benzoate)/5 ml
Nitrofurantoin
tablet, 100 mg
spectinomycin *
powder for injection, 2 g (as hydrochloride) in vial: Could become SAD
sulfamethoxazole + trimethoprim
tablet, 400 mg + 80 mg; 800mg +160mg, oral suspension, 200 mg + 40 mg/5 ml; injection, 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules

6.2.3 Antileprosy medicines

Rifampicin
capsule or tablet, 150 mg, 300 mg

6.2.4 Antituberculosis medicines

ethambutol
tablet, 400 mg (hydrochloride)
isoniazid
tablet, 100 -300 mg
pyrazinamide
tablet, 400 mg
6.2.4 Antituberculosis medicines

rifampicin
capsule or tablet, 150 mg, 300 mg

Streptomycin
powder for injection, 1 g (as sulfate) in vial

6.3 Antifungal medicines

fluconazole
capsule 200 mg, 150 mg; injection 2 mg/ml in vial; oral suspension 50 mg/5-ml (widely requested): Should be seriously considered

Griseofulvin capsule
or tablet, 500 mg, suspension 10 mg/ml

Nystatin
tablet, 100 000, 500 000 IU; lozenge 100 000 IU;

pessary, 100 000 IU, vaginal cream, topical cream.
Lozenges and or tablets really needed to reduce cost, and improve compliance

Ketoconazole (nhi)
Tablet, 200 mg SAD

Clotrimazole
Cream, 1%, cream vaginal 2%, tablets, 500 mg,

Miconazole
Cream, 1%

amphotericin B
powder for injection, 50 mg in vial: Needed for critical cases - SAD

Flucytosine
Injection 2.5 G SAD/NO STOCK

6.4 Antiviral medicines

6.4.1 Antitherpes medicines

aciclovir
tablet, 400 mg; powder for injection 250 mg (as sodium salt) in vial, eye ointment ophthalmic 3%, topical 5%

Oseltamivir
Capsule, 75 mg, suspension, 60 mg/5 ml

INFLUNZA PANDEMIC Consideration for the Avian Influenza

6.4.2 Antiretrovirals

6.4.2.1 Nucleoside reverse transcriptase inhibitors

abacavir (ABC)
oral solution, 100 mg (as sulfate)/5 ml

didanosine (ddI)
powder for oral solution, 2 G/bottle

lamivudine (3TC)

6.4.2 Antiretrovirals

- Stavudine (d4T) tablet, 150mg, or oral solution 50 mg/5ml
- Zidovudine (ZDV or AZT) capsule, 30mg, or oral solution, 5mg/5ml
- Lamivudine/zidovudine tablets, 150mg/300mg

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

- Efavirenz (EFV or EFZ) capsule, 600mg or oral solution, 150mg/5ml
- Nevirapine (NVP) tablet 200mg; or oral suspension 50mg/5ml

6.4.2.3 Protease inhibitors

- Indinavir (IDV) capsule, 400mg (as sulfate)
- Ritonavir capsule, 100mg
- Lopinavir + Ritonavir (LPV/r) Suspension, 20mg/80mg; 160mls

6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines
- Metronidazole tablet, 200-500mg; injection, 500mg in 100ml vial; oral suspension 200mg (as benzoate)/5ml
- Tinidazole Tablet, 500mg

6.5.2 Antileishmaniasis medicines
- Pentostam (stibogluconate) Powder for injection, 100mg/ml

6.5.3 Antimalarial medicines

6.5.3.1 For curative treatment

Medicines for the treatment of malaria cases should be used in combination.
- Chloroquine tablet 200mg, 250mg (as phosphate or sulfate); syrup
- Primaquine tablet, 7.5mg, 15mg (as diphosphate)
6.5.3 Antimalarial medicines

6.5.3.2 For prophylaxis

Chloroquine
tablet, 150 mg (as phosphate or sulfate);
Doxycycline
capsule or tablet, 100 mg (hydrochloride)

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

Ergotamine/caffeine *(Cafergot)*
tablet, 1 mg (tartrate)* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.
Paracetamol
tablet, 500 mg
Sumatriptan (imigran) Tablet, 50mg: Really Needed; quick and prolonged action – Very good prognosis

7.2 For prophylaxis

propranolol
tablet, 20 mg, 40 mg (hydrochloride)

8. ANTINEOPLASTIC, IMMUNOSUPPRESSIVES AND MEDICINES USED IN PALLIATIVE CARE

8.1 Immunosuppressive medicines

Azathioprine
tablet, 50 mg; powder for injection, 100 mg (as sodium salt) in vial
Ciclosporin
capsule, 25 mg; concentrate for injection 50 mg/ml in 1-ml ampoule for organ transplantation SAD

8.2 Cytotoxic medicines

Cyclophosphamide
tablet, 25 mg; powder for injection, 500 mg in vial
Fluorouracil
injection, 50 mg/ml in 5-ml ampoule
Methotrexate
tablet, 2.5 mg (as sodium salt); powder for injection, 50 mg (as sodium salt) in vial
tamoxifen
Tablet, 20mg
8.3 Hormones and antihormones

8.4 Medicines used in palliative care

9. ANTIPARKINSONISM MEDICINES

biperiden
tablet, 2 mg, 4 mg (hydrochloride);
Benzhexol (Trihexyphenidyl)
Tablet, 2mg, 5mg
procyclidine
Inj, 5mg/ml; 2ml
levodopa + carbidopa
tablet, 100 mg + 25 mg; 100mg +10mg; 250 mg + 25 mg

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines

ferrous salt
tablet, equivalent to 65 mg iron; oral solution equivalent to 30 mg iron (as sulfate)/ml
ferrous salt + folic acid
tablet equivalent to 60 mg iron + 25mg folic acid (nutritional supplement for use during pregnancy.)
folic acid
tablet 1mg; 5mg
Hydroxocobalamin
injection, 1 mg in 1-ml ampoule

10.2 Medicines affecting coagulation

heparin sodium
injection, 10000 IU/ml, in 5-ml ampoule
Phytomenadione
injection,K1 1mg/ml;1ml; K10, 10 mg/ml in 5-ml am-
poule;
protamine sulphate
injection, 10 mg/ml in 5-ml ampoule
warfarin
tablet, 5 mg (sodium salt)

11. BLOOD PRODUCTS AND PLASMA SUB-
STITUTES

11.1 Plasma substitutes
11. Blood Products and Plasma Substitutes

11. Blood Products and Plasma Substitutes

**dextran 70**
injectable solution, 6% in 5% dextrose
**plasma protein fraction** (human)
5%, 250ml

11.2 Plasma fractions for specific use


**factor VIII concentrate**
dried*
the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee. (rare disease)

**factor IX complex coagulation factors, II, VII, IX, X) concentrate** *
dried* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee. (rare disease)

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

**atenolol**
tablet, 50 mg, 100 mg
**glyceryl trinitrate**
tablet (sublingual), 500 micrograms; spray 400 micrograms
**isosorbide dinitrate tablet** (sublingual), 10 mg
**verapamil** tablet, 80 mg, 120 mg (hydrochloride); inj 75 mg/ml
**diltiazem**
Tablet, 60mg

12.2 Antiarrhythmic medicines

**atenolol**
tablet, 50 mg, 100 mg
**Digoxin**
tablet, 0.125 mg, 0.25 mg; oral solution 50 micrograms/ml; injection 0.25mg/ml in 2-ml ampoule
12.2 Antiarrhythmic medicines

**epinephrine** (adrenaline)
- injection, 1 mg (as hydrochloride)/ml in ampoule

**Lidocaine**
- injection, 4%; 2ml amp

**Verapamil**
- tablet, 40 mg, 80 mg (hydrochloride); injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule

**quinidine**
- tablet, 200 mg (sulfate)* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

**disopyramide**
- Tab, 100mg

12.3 Antihypertensive medicines

**qatenolol**
- tablet, 50 mg, 100 mg

**captopril**
- Tablet, 25mg, 12.5mg

**qenalapril**
- tablet, 5 mg, 20mg

**labetolol**
- Injection, 5mg/ml; 20ml

**minoxidil**
- Tablet, 5mg: *Very small quantity needed for hypertensive urgency*

**propranolol**
- Tablet, 40mg,

**sodium nitropruside w/solv.**
- Injection, 50mg/2ml

**hydralazine**
- tablet, 25 mg, (hydrochloride); powder for injection, 20 mg (hydrochloride) in ampoule* hydralazine is listed for use in the acute management of severe pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

**hydrochlorothiazide**
- scored tablet, 50 mg, 25 mg (most patients use this strength)

**Furosemide** (lasix)
- Tablet, 40mg, injection 10mg/ml; 2ml

**methyldopa** *
- tablet, 250 mg* methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

evidence of efficacy and safety of other medicines.

nifedipine *
sustained release formulations, tablet 10 mg* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

amlodipine
Tablet, 5mg

prazocin hydrochloride
Tablet, 1mg

losartan (cozaar)
tablet, 25mg, 50mg SAD

nimodipine
Capsule, 30 mg SAD

metoprolol
Tablet, 50 mg, 100mg, inj 1mg/ml -5ml ampoule SAD

sodium nitroprusside
powder for infusion, 50 mg in ampoule; Small quantity needed for hypertensive Emergency

12.4 Medicines used in heart failure

Digoxin
tablet, 62.5 micrograms, 250 micrograms; oral solution, 50 micrograms/ml; injection, 250 micrograms/ml in 2-ml ampoule

enalapril
tablet, 2.5 mg

hydrochlorothiazide
scored tablet, 25 mg

Dopamine
injection, 40 mg (hydrochloride) in 5-ml vial: Should be formulary drug

12.5 Antithrombotic medicines

acetylsalicylic acid
tablet, 81 mg

dipyridamole
Tablet, 25 mg

Streptokinase
powder for injection, 1.5 million IU in vial SAD

12.6 Lipid-lowering agents

simvastatin
tablet, 10mg, 20mg

gemfibrozil
Tablet 300mg, 600mg

niacin
Tablet 600mg

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

benzoic acid + salicylic acid (whitfield oint.)
ointment, 6% + 3%
miconazole
ointment or cream, 2% (nitrate)
clotrimazole
Cream, 1%
ketoconazole
Tablet, 200mg

nystatin topical cream
Ointment, 10%

13.2 Anti-infective medicines

methylrosanilinium chloride (gentian violet)
aqueous solution, 0.5%;
tincture, 0.5%
neomycin sulfate + bacitracin ointment,
5 mg
neomycin sulfate + 500 IU bacitracin
zinc/g
potassium permanganate
aqueous solution 1:10 000
silver sulfadiazine
cream, 1%, in 500-g container
Acriflavine solution
Soln, 0.1%
Chlorhexidine
Solution, 20%

13.3 Anti-inflammatory and antipruritic medicines

betamethasone
ointment or cream, 0.1% (as valerate) SAD
calamine lotion
Lotion 4%

hydrocortisone
ointment or cream, 1% (acetate)
13.3 Anti-inflammatory and antipruritic medicines

haemorrhoidal preparations with steroid
Cream, ointment

13.4 Astringent medicines

Zinc oxide
Cream, 15G

13.5 Medicines affecting skin differentiation and proliferation

podophyllum resin
solution, 10-25%

13.6 Scabicides and pediculicides

benzyl benzoate
lotion, 25%
lindane Cream,
1%, 50G, shampoo, 1% x 200mls, lotion 1%
Permethrin
cream 5%; lotion 1%

14. DIAGNOSTIC AGENTS

barium sulphate
aqueous suspension

15. DISINFECTANTS AND ANTISEPTICS

15.1 Antiseptics
chlorhexidine
solution, 5% (digluconate) for dilution
ethanol
solution, 70% (denatured)
polyvidone iodine
solution, 10%
cetrimide
Solution, 20%
hydrogen peroxide  3%(gallon), 6%

15.2 Disinfectants

chlorine base compound (EUSOL)
powder (0.1% available chlorine) for solution
Glutaral (Cidex Plus)
solution, 2%
16. DIURETICS

furosemide
tablet, 40 mg; injection 10 mg/ml in 2-ml ampoule
hydrochlorothiazide
scored tablet, 25 mg
mannitol
injectable solution, 20%
Spironolactone
tablet, 25 mg
Bumetamide
Tablet, 1 mg

17. GASTROINTESTINAL MEDICINES

17.1 Antacids and other antiulcer medicines

Aluminium/magnesium hydroxide
tablet, 300 mg; oral suspension, 320 mg/5 ml
ranitidine
tablet, 150 mg (as hydrochloride); oral solution 75 mg/5-ml; injection, 25 mg/ml in 2-ml ampoule
Omeprazole
Tablet, 20 mg, injection 40 mg
dimenhydrinate
Tablet, suppository 50 mg

17.2 Antiemetic medicines

Metoclopramide
tablet, 10 mg (hydrochloride); injection, 5 mg (hydrochloride)/ml in 2-ml ampoule, solution, 5 mg/5 ml
Promethazine
tablet, 25 mg (hydrochloride); injection, 25 mg (hydrochloride)/ml in 2-ml ampoule

17.3 Antihaemorrhoidal medicines

local anaesthetic, astringent and anti-inflammatory medicine *Xyloproct
ointment or suppository* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.
Anusol
Suppositories and cream:
Small Quantity needed for haemorrhoids
Preparation-H
17.3 Antihaemorrhoidal medicines

Cream: Small Quantity needed for haemorrhoids

17.4 Anti-inflammatory medicines

sulfasalazine
tablet, 500 mg; suppository 500 mg; retention enema
Triamcinolone Acetonide
Injection, 40 mg/ml

17.5 Antispasmodic medicines

hyoscinebutyl bromide
Tablet 10 mg, injection 20 mg/ml; 1 ml
atropine*
injection, 0.6 mg (sulfate) in 1-ml ampoule
*
the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

17.6 Laxatives

Bisacodyl
Tablet, 5 mg, suppository 5 mg, 10 mg

17.7.1 Oral Rehydration

oral rehydration salts * (for glucose-electrolyte solution)
glucose: 75 mEq
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

+ 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. * in cases of cholera a higher concentration of sodium may be required.
17.7.2 Antidiarrhoal (symptomatic) medicines

Loperamide
Tablet, 2mg

18. HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes

Addison’s disease is a rare condition; adrenal hormones are already included in section 3.

18.2 Androgens

18.3 Contraceptives

18.3.1 Hormonal contraceptives

noretinisterone enantate
tablet, 5mg

medroxyprogesterone acetate
depot injection, 150 mg/ml in 1-ml vial

diethylstibestrol
Tablet 5 mg

18.3.3 Barrier methods

condoms

18.5 Insulins and other antidiabetic agents

glibenclamide
tablet, scored, 5 mg

insulin injection (soluble)
injection, 100 IU/ml in 10-ml vial

intermediate-acting insulin Isophane (NPH)
injection, 100 IU/ml in 10 ml vial (as compound insulin zinc suspension or isophane insulin)

Isophane 70/30
Injection, 100 IU in 10mls

Metformin
tablet, 500 mg (hydrochloride)

18.6 Ovulation inducers
18.7 Progestogens

Norethisterone
tablet, 5 mg

medroxyprogesterone acetate *
tablet, 5 mg* the public health relevance and/or efficacy
and/or safety of this item has been questioned and its
continued inclusion on the list will be reviewed at the
next meeting of the Expert Committee.

18.8 Thyroid hormones and antithyroid medicines

Levothyroxine
tablet, 100 micrograms (sodium salt)
potassium iodide
tablet, 60 mg
carbimazole
Tablet 5mg
propylthiouracil
tablet, 50 mg

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO Require-
ments for Tuberculins (Revised 1985). WHO Expert
Committee on Biological Standardization Thirty-sixth
Annex 1).

tuberculin,
purified protein derivative (PPD)
Injection

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO
Requirements for the Collection, Processing and Qual-
ity Control of Blood, Blood Components and Plasma
Derivatives (Revised 1992). WHO Expert Committee
on Biological Standardization Forty-third report, (WHO

anti-D immunoglobulin (human Rhogam)
injection, 200 IU/2ML in single-dose vial
antitetanus immunoglobulin (human)
injection, 500 IU in vial
antivenom serum *

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19.2 Sera and immunoglobulins

Injection, 50,000IU/VIAL/10mls* exact type to be defined locally
diphtheria antitoxin
injection, 10 000 IU, 20 000 IU in vial
rabies immunoglobulin
injection, 150 IU/ml in vial

19.3 Vaccines

All vaccines should comply with the WHO Requirements for Biological Substances.

19.3.1 For universal immunization

BCG vaccine
diphtheria vaccine
hepatitis B vaccine
Hepatitis C vaccine
measles vaccine
pertussis vaccine
poliomyelitis vaccine
Tetanus vaccine

19.3.2 For specific groups of individuals

influenza vaccine
meningococcal meningitis vaccine
mumps vaccine
rabies vaccine (inactivated: prepared in cell culture)
Rubella vaccine
typhoid vaccine
Yellow fever vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY ACTING) AND CHOLINESTERASE INHIBITORS

Neostigmine tablet,
15 mg (bromide); injection, 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule
suxamethonium
injection, 50 mg (chloride)/ml in 2-ml ampoule; powder for injection (chloride), in vial
Dantrolene
Injection, 20mg, 10mg
Pancuronium bromide
Inj, 2 mg/ml; 2ml
Atracurium besylate
Injection, 50mg
20. Muscle Relaxants (Peripherally acting) and Cholinesterase Inhibitors

Orphenadrine
Tablet, 100mg

Pyridostigmine
tablet, 60 mg (bromide); injection, 1 mg in 1-ml ampoule, syrup

Mevacurium
Injection 2mg/ml 5-ml amp  SAD

21. OPHTHALMOLOGICAL and ENT PREPARATIONS

21.1 Anti-infective agents

gentamicin *
solution (eye drops), 0.3%/10ml (sulfate) * final selection depends on indication for use

chloramphenicol
Eye drops, 0.5%/10mls, ointment, 1%

chloramphenicol + prednisone acetate
Solution, 2.5+5mg/ml

cyclopentolate
Ophthalmic drops, 0.5%/10ml

acyclovir
Ophthalmic drops, 3%

tetracycline
eye ointment, 1% (hydrochloride)

hydrocortisone
Ophthalmic ointment, 1%

betaxolol
Ophthalmic, 0.50%

neomycin/ polymixin/hydrocortisone
(Cortisporin)
Otic drops, 0.35%/10,000/1%

ciprofloxacin
Otic drops, 0.2%

oxymetazoline
Nasal drops, 0.5% x 10ml or x 20ml

21.2 Anti-inflammatory agents

prednisolone
solution (eye drops), 0.5% (sodium phosphate)

21.3 Local anaesthetics

tetracaine
solution (eye drops), 0.5% (hydrochloride)

21.4 Miotics and antiglaucoma medicines

Acetazolamide
tablet, 250 mg

Pilocarpine
solution (eye drops), 2%, 4% (hydrochloride or nitrate)

Timolol
solution (eye drops), 0.25%, 0.5% (as maleate)

21.5 Mydriatics

Atropine
solution (eye drops), 0.1%; 0.5%, 1% (sulfate)

Homatropine
Ophthalmic drop, 2%

22. OXYTOCICS AND ANTIOXYTOCICS

22.1 Oxytocics

 Ergometrine * tablet, 500 micrograms (hydrogen maleate); injection, 500 micrograms (hydrogen maleate) in 1-ml ampoule,* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

Magnesium sulphate
500mg/ml, 2ml

Oxytocin
injection, 10 IU in 1-ml ampoule, 5IU in 1ml ampoule

22.2 Antioxytocics

Ritodrine
injection 10mg/ml, 5-ml amp

23. PERITONEAL DIALYSIS SOLUTION

Complementary List
intraperitoneal dialysis solution (of appropriate composition)
parenteral solution
24. PSYCHOTHERAPEUTIC MEDICINES

24.1 Medicines used in psychotic disorders

chlorpromazine
tablet, 50mg, 100 mg (hydrochloride); injection, 25 mg (hydrochloride)/ml in 2-ml ampoule

fluphenazine
injection, 25 mg (decanoate or enantate) in 1-ml x 10ml vial

haloperidol
tablet, 5 mg; injection, 5 mg in 1-ml x 2ml ampoule

thioridazine
Tablet, 25mg, 100mg,

flupenthixol
Tablet, 1mg

trifluperazine (stelazine)
Tablet, 5mg

resperidone
Tablets, 2mg, injection 25 mg/ vial

quetiapine
Tablet, 50 mg, 200 mg

clozapine
tablet, 25 mg, 50 mg, 100 mg

24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

amitriptyline
tablet, 25 mg, 75mg (hydrochloride)

sertraline
Tablet, 50mg

fluoxetine
Tablet, 20mg

imipramine
Tablets, 25mg

24.2.2 Medicines used in bipolar disorders

Carbamazepine
scored tablet, 200 mg

lithium carbonate
capsule or tablet, 300 mg

valproic acid
enteric coated tablet, 200 mg, or 250 mg (sodium salt)
24.3 Medicines used in generalized anxiety and sleep disorders

diazepam
scored tablet, 5 mg, injection, 5mg/ml
clonazepam
Tablets, 1mg
lorazepam
Tablets, 1mg, injection 4 mg/ml
alprazolam
Tablets, 0.25mg
diphenhydramine
Tablet, 25mg, 50mg, injection, 25mg, 50mg

24.4 Medicines used for obsessive compulsive disorders and panic attacks
Clomipramine
capsules, 10 mg, 25 mg (hydrochloride)
Ritalin (methylphenidate)
Tablets, 10mg, 20mg, SR

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

Antiasthmatic and medicines for chronic obstructive pulmonary disease
beclometasone
inhalation (aerosol), 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose
epinephrine (adrenaline)
injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
ipratropium bromide
inhalation (aerosol), 20 micrograms/metered dose
salbutamol
tablet, 2 mg, 4 mg (as sulfate); inhalation (aerosol), 100 micrograms (as sulfate) per dose; syrup, 2 mg/5 ml; injection, 50 micrograms (as sulfate)/ml in 5-ml ampoule; respirator solution for use in nebulizers, 5 mg (as sulfate)/ml
theophylline *
tablet, 125 mg, 250 mgSR* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.
Leukotriene receptors
montelukast

tablets, 10mg
Prednisolone
Syrup, 15mg/5ml x 60ml

Complementary List
aminophylline*
injection, 25 mg/ml in 10 ml ampoule*
the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

Salmeterol
Long acting: Consider for inclusion = Compliance enhancement
advantan (methylprednisolone acetonide)
ointment, 30G

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES

26.1 Oral

oral rehydration salts (for glucose-electrolyte solution) see section 17.7.1
Calcium gluconate/lactate
Tablet, 300mg, inj 100mg/ml, 10ml
Sodium bicarbonate
Inj, 8.4%; 10ml amp
potassium chloride powder for solution

26.2 Parenteral

Glucose (Detrose)
injectable solution, dextrose, 5%, 10% isotonic; 50% hypertonic
Hypokalisal B
Injection, 250ml
potassium chloride solution, 2mEq/ml; 10ml 11.2% in 20-ml ampoule, (equivalent to K+ 1.5 mmol/ml, Cl- 1.5 mmol/ml)
Sodium chloride
injectable solution, (normal saline) 0.9% isotonic (equivalent to Na+ 154 mmol/l, Cl- 154 mmol/l)
Sodium hydrogen carbonate (Sodium bicarbonate)
injectable solution, 1.4% isotonic (equivalent to Na+ 154 mmol/l, Cl- 154 mmol/l)
167 mmol/l, HCO₃⁻ 167 mmol/l); solution, 8.4% in 10-ml ampoule (equivalent to Na⁺ 1000 mmol/l, HCO₃⁻1000 mmol/l)

sodium lactate, compound solution
injectable solution (Hartmann’s soln) B.P

26.3 Miscellaneous

water for injection,
100-ml ampoules

27. VITAMINS AND MINERALS

Iodine
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; capsule, 200 mg.

Pyridoxine (vitamin B6)
tablet, 50 mg (hydrochloride)
retinol
sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg); capsule, 200 000 IU (as palmitate) (110 mg); oral oily solution 100 000 IU (as palmitate)/ml in multidose dispenser; water-miscible injection 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule

Riboflavin (vitamin B2)
tablet, 5 mg
Thiamine (vitamin B1)
tablet, 50 mg (hydrochloride); inj 100mg/ml

Cyanocobalamine (Vit. B12)
Injection, 10mL

Vitamin B complex
Injection

Complementary List
calcium gluconate *
injection, 100 mg/ml in 10-ml ampoule* the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

Multivitamines
Tablets, Chewable tablets and Syrups
SECTION II

DRUG MONOGRAPHS
ORGANIZATION OF MONOGRAPH

The monograph section is organized according to the pharmacologic/therapeutic classification developed and adopted by the Belize Formulary Committee. This is an adaptation of the classification system employed by the American Hospital Formulary Service (AHFS).

Each pharmacologic/therapeutic classification/heading contains a GENERAL STATEMENT, when applicable, and the individual DRUG MONOGRAPHS in alphabetical order.

The GENERAL STATEMENT provides an orientation to the disease states commonly treated by the drugs within each therapeutic/pharmacologic heading. This section presents guidelines for treatment approaches and in some cases cost and therapeutic comparisons.

The DRUG MONOGRAPHS are presented after each general statement and contain information that is organized in the following manner:

Monograph Title and Synonyms: The nonproprietary (generic) name of the drugs as listed in the British National Formulary (BNF) and the USP, and common abbreviations

Indications: The most common uses of the drug

Cautions:

Contraindications: Patient types, disease states or conditions where the drug should never be used

Precautions: Patient types, disease states or conditions where special precautions should be taken if the drug is used (e.g. reduce dosage, monitor patient closely, consider using other therapeutic agent). This subsection may also contain other information such as “avoid contact with skin”.

Adverse Reactions: The “side effects”, “toxic effects”, or “unwanted effects” which are caused by the drug frequently and/or cause serious harm. This is by no means a complete listing of all possible adverse reactions.

Drug Interactions: The established or probable clinically significant drug/drug interactions that occur when the two agents are used concomitantly. Suspected drug interactions or those of minor clinical significance are not included.

Use during Pregnancy/Lactation: *The possibility of risk to the fetus during pregnancy is placed into one of
the following categories with increasing level of risk:

1. "No evidence of adverse fetal effects": Studies have been conducted and no clear teratogenicity has been demonstrated.

2. "Potential fetal risk": Teratogenicity has been demonstrated in animals but not in humans or there is a theoretical risk in humans but this has not been proven.

3. "High risk to fetus": Teratogenicity has been proven and the drug should only be used if the seriousness of the pregnant mothers condition outweighs the potential risk to the fetus.

4. "Do not use": Teratogenicity has been proven and there is no clinical situation that justifies the use of this drug in pregnant mothers.

Information on lactation is reported in the monographs in the following order of increased risk to the infant:

1. "Not excreted in breast milk"

2. "No evidence of adverse effects to the infant"

3. "Potential risk to the infant"

4. "Avoid use of the drug or discontinue breastfeeding"

* Note: Also see Section II: Guide to Rational Prescribing, under the headings of Prescribing During Pregnancy and Prescribing During Lactation, for general guidelines.

Advice to the Patient: Special information to be communicated during the patient consultation. This does not include information which is already stated in the Cautions section. This does not include all the common information that should be given such as: shake well, take four times daily, finish all of the prescription, etc.

Dosage and Administration: The most common dosage ranges for the most common disease states for which the drug is used. Paediatric dosages are generally for children older than 1 year and not for infants. Some information on mixing, compatibility, or administration may be included. In some cases information for dosage adjustment in patients with renal impairment is included. Also see section II for more information on prescribing in renal disease.

Preparations: Includes dosage forms, strength, and sizes adopted by the Belize Formulary Committee. Many others may exist.

Common Brand Name(s): Partial listing of brand names which are likely to be encountered in the Caribbean and Central America.
Section 1: Drugs used in anaesthesia

1.1 General anesthetic and oxygen
1.1.1 Intravenous agents
1.1.2 Volatile inhalation gases
1.2 Local anesthetic
1.3 Preoperative medication and sedation
1.4 Muscle relaxants and cholinesterase inhibitors
1.5 Analgesic and opioid antagonists
1.6 Blood substitutes and solution for correcting fluid imbalance
This section describes drugs used in anaesthesia. To produce a state of prolonged full surgical anaesthesia reliably and safely, a variety of drugs is needed. Special precautions and close monitoring of the patient are required. These drugs may be fatal if used inappropriately and should be used by non–specialized personnel only as a last resort. Irrespective of whether a general or conduction (regional or local) anaesthetic technique is used, it is essential that facilities for intubation and mechanically assisted ventilation are available. A full preoperative assessment is required including, if necessary, appropriate fluid replacement.

Anaesthesia may be induced with an intravenous barbiturate, parenteral ketamine, or a volatile agent. Maintenance is with inhalational agents often supplemented by other drugs given intravenously. Specific drugs may be used to produce muscle relaxation. Various drugs may be needed to modify normal physiological functions or otherwise to maintain the patient in a satisfactory condition during surgery.

LONG-TERM MEDICATION
The risk of stopping long-term medication before surgery may be greater than the risk of continuing it. It is essential that the anaesthetist is told of all drugs that the patient is (or has been) taking; for further advice see section 10.2 (oral anticoagulants), section 18.1 (corticosteroids), section 18.3.1 (hormonal contraceptives), and section 18.7 (diabetic patients).

1.1 General anaesthetics and oxygen

1.1.1 Intravenous agents

Intravenous anaesthetics may be used alone to produce anaesthesia for short surgical procedures but are more commonly used for induction only. They can produce apnoea and hypotension and thus facilities for adequate resuscitation must be available. They are contraindicated if the anaesthetist is not confident of being able to maintain an airway. Before intubation is attempted, a muscle relaxant must be given. Individual requirements vary considerably; lesser dosage is indicated in the elderly, debilitated or hypovolaemic patients. Intravenous induction using thiopental is rapid and excitement does not usually occur. Anaesthesia persists for about 4–7 minutes; large or repeated doses severely depress respiration and delay recovery.

Anaesthesia with ketamine persists for up to 15 minutes after a single intravenous injection and is characterized by profound analgesia. It may be used as the sole agent for diagnostic and minor surgical interventions. Subanaesthetic concentrations of ketamine may be used to provide analgesia for painful procedures.
procedures of short duration such as the dressing of burns, radiotherapeutic procedures, marrow sampling and minor orthopaedic procedures. Recovery from ketamine anaesthesia is associated with a high incidence of hallucinations and other emergence reactions. Ketamine is of particular value in children, in whom hallucinations are believed to be less significant.

**Propofol** is associated with rapid recovery without hangover effect and is widely used. There is sometimes pain on intravenous injection, but significant extraneous muscle movements do not occur. Convulsions, anaphylaxis and delayed recovery from anaesthesia have occurred after propofol administration. Propofol has been associated with bradycardia, occasionally profound; intravenous administration of an antimuscuranic may be necessary to prevent this.

**THIOPENTAL SODIUM**

Thiopental is a representative intravenous anaesthetic. Various drugs can serve as alternatives

*Injection* (Powder for solution for injection), thiopental sodium, 0.5-g and 1-g ampoules

**Uses:**
induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration

**Contraindications:**
inability to maintain airway; hypersensitivity to barbiturates; cardiovascular disease; dyspnoea or obstructive respiratory disease; porphyria

**Precautions:**
local extravasation can result in extensive tissue necrosis and sloughing; intra-arterial injection causes intense pain and may result in arteriospasm; hepatic impairment (Appendix 5); pregnancy (Appendix 2); **interactions:** Appendix 1

**Patient advice:**
Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours and also to avoid alcohol for 24 hours

**Dosage:**
Induction, *by intravenous injection* as a 2.5% (25 mg/ml) solution over 10–15 seconds, **Adult** 100–150 mg (reduced in elderly or debilitated patients), followed by a further 100–150 mg if necessary according to response after 60 seconds; or up to 4 mg/kg; **Child** 2–7 mg/kg repeated if necessary according to response after 60 seconds

**Reconstitution**
Solutions containing 25 mg/ml should be freshly prepared by mixing 20 ml of water for injections with the contents of the 0.5-g ampoule or 40 ml with the 1-g ampoule. Any solution made up over 24 hours previously or in which cloudiness, precipitation

or crystallization is evident should be discarded

**Adverse effects:**
- rapid injection may result in severe hypotension and hiccup;
- cough, laryngeal spasm, allergic reactions

**KETAMINE**

_Injection_ (Solution for injection), ketamine (as hydrochloride)

50 mg/ml, 10-ml vial

**Uses:**
- induction and maintenance of anaesthesia; analgesia for painful procedures of short duration

**Contraindications:**
- thyrotoxicosis; hypertension (including pre-eclampsia); 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

**Precautions:**
- supplementary analgesia often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice); during recovery, patient must remain undisturbed but under observation; pregnancy (Appendix 2); **interactions:** Appendix 1

**Patient advice.** Warn patient not to perform skilled tasks, for example operating machinery or driving, for 24 hours and also to avoid alcohol for 24 hours

**Dosage:**
- Induction, _by intramuscular injection_, **Adult** and **Child** 6.5–13 mg/kg (10 mg/kg usually produces 12–25 minutes of anaesthesia)
- Induction, _by intravenous injection_ over at least 1 minute, **Adult** and **Child** 1–4.5 mg/kg (2 mg/kg usually produces 5–10 minutes of anaesthesia)
- Induction, _by intravenous infusion_ of a solution containing 1 mg/ml, **Adult** and **Child** total induction dose 0.5–2 mg/kg; maintenance (using microdrip infusion), 10–45 micrograms/kg/minute, rate adjusted according to response
- Analgesia, _by intramuscular injection_, **Adult** and **Child** initially 4 mg/kg

**DILUTION AND ADMINISTRATION:**
- According to manufacturer’s directions

**Adverse effects:**
- hallucinations and other emergence reactions during recovery possibly accompanied by irrational behaviour (effects rarely persist for more than few hours but can recur at any time within 24 hours); transient elevation of pulse rate and blood pressure common, arrhythmias have occurred; hypotension and bradycardia occasionally reported

**PROPOFOL**
Injection (emulsion), propofol 10 mg/ml, 20 ml

Uses:
Induction and maintenance of general anaesthesia.

Contraindications:
Not to be used for the sedation of ventilated children and adolescents under 17 years (risk of potentially fatal effects including metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidaemia and hepatomegaly)

Precautions:
Convulsions, anaphylaxis and delayed recovery from anaesthesia have occurred after prolonged administration. Monitor blood pressure if risk of fat overload if sedation longer than 3 days

Dosage:
1% injection

Induction of anaesthesia by intravenous injection or infusion, 1.5-2.5 mg/kg (less in those over 55 years) at a rate of 20-40 mg every 10 seconds; CHILD over 1 month, administer slowly until response (usual dose in child 8 years 2.5 mg/kg, may need more in younger child e.g. 2.5-4 mg/kg)

Maintenance of anaesthesia by intravenous injection, 25-50 mg repeated according to response or by intravenous infusion, 4-12 mg/kg/hour, CHILD over 3 years, by intravenous injection or infusion, 9-15 mg/kg/hour (Note, Propofol-Lipuro may be used for the maintenance of anaesthesia in CHILD over 1 month, by IV infusion, 9-15 mg/kg/hour)

Sedation in intensive care, by intravenous infusion, ADULT over 17 years, 0.3-4 mg/kg/hour.

Sedation for surgical and diagnostic procedures, initially by intravenous injection over 1-5 minutes, 0.5-1 mg/kg; maintenance, by IV infusion, 1.5-1.5-4.5 mg/kg/hour (additionally, if rapid increase in sedation required, by IV injection, 10-20 mg); those over 55 years may require lower dose; CHILD and ADOLESCENT under 17 years not recommended

2% injection

Induction of anaesthesia by intravenous injection or infusion, 1.5-2.5 mg/kg (less in those over 55 years) at a rate of 20-40 mg every 10 seconds; CHILD over 3 years administer slowly until response (usual dose in child 8 years 2.4 mg/kg, may need more in younger child e.g. 2.4-4 mg/kg)

Maintenance of anaesthesia, by intravenous infusion, 4-12 mg/kg/hour, CHILD over 3 years, by IV infusion, 9-15 mg/kg/hour

Sedation in intensive care, by intravenous infusion, ADULT
over 17 years, 0.3-4 mg/kg/hour

**Adverse effects:**
Bradydcardia, occasionally profound (administration of an antimuscarinic may be necessary to prevent this). Pulmonary oedema, and postoperative fever have been reported.

1.1.2 **Volatile inhalational agents**

One of the volatile anaesthetics, isoflurane, sevoflurane, halothane (with or without nitrous oxide), must be used for induction when intravenous agents are contraindicated and particularly when intubation is likely to be difficult.

If intubation is likely to be difficult, halothane is preferred. It does not augment salivary or bronchial secretions and the incidence of postoperative nausea and vomiting is low. Severe hepatitis, which may be fatal, sometimes occurs; it is more likely in patients who are repeatedly anaesthetized with halothane within a short period of time.

Isoflurane is a volatile anaesthetic similar to halothane but less potent. Heart rhythm is generally stable during isoflurane anaesthesia, but heart-rate may rise particularly in younger patients. Systemic pressure may fall, owing to decrease in systemic vascular resistance and with less cardiac output than occurs with halothane. Respiration is depressed. Muscle relaxation is produced and muscle relaxant drugs potentiated. Isoflurane may also cause hepatotoxicity in those sensitised to halogenated anaesthetics but the risk is appreciably smaller than with halothane.

Sevoflurane is a rapid acting volatile anaesthetic. Patients may require early postoperative pain relief as emergence and recovery are particularly rapid. Sevoflurane can interact with carbon dioxide absorbents to form compound A, a potentially nephrotoxic vinyl ether. However, in spite of extensive use, no cases of sevoflurane-induced permanent renal have been reported.

**HALOTHANE**

*Volatile liquid*

**Uses:**
induction and maintenance of anaesthesia

**Contraindications:**
history of unexplained jaundice or pyrexia 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 (at least 3 months should be allowed to elapse between each re-exposure); avoid for dental procedures in patients under 18 years unless treated in hospital (high risk of arrhythmias); pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

Dosage:
Induction, using specifically calibrated vaporizer, gradually increase inspired gas concentration to 2–4% (ADULT) or 1.5–2% (CHILD) in oxygen or nitrous oxide–oxygen
Maintenance, ADULT and CHILD 0.5–2%

Adverse effects:
arrhythmias; bradycardia; respiratory depression; hepatic damage

ISOFLURANE*

Inhalation, Volatile liquid

Uses:
Induction and maintenance of anaesthesia

Contraindications:
Susceptible to malignant hyperthermia

Precautions:
Patients with arrhythmia, pregnancy, bradycardia, hypotension, arrhythmias, respiratory depression

Dosage:
Induction, using specifically calibrated vaporizer, gradually increase inspired gas concentration to 2.5–5% (ADULT) or 1.5–2% (CHILD) in oxygen or nitrous oxide–oxygen
Maintenance, ADULT and CHILD 0.5–2%

Adverse effects:
Arrhythmias; bradycardia; respiratory depression; hepatic damage

SEVOFLURANE

Inhalation, Volatile liquid

Uses:
Induction and maintenance of anaesthesia

Contraindications:
Susceptibility to malignant hyperthermia

Precautions:
Renal impairment, sevoflurane can interact with carbon dioxide absorbents to form compound A, a potentially nephrotoxic vinyl ether

Dosage:
Using a specifically calibrated vaporizer, Induction, up to 5% in oxygen or nitrous oxide–oxygen, (CHILD) up to 7%
Maintenance, ADULT and CHILD 0.5–2%

Adverse effects:
Arrhythmias; bradycardia; respiratory depression; hepatic damage

INHALATIONAL GASES

Nitrous oxide is used for the maintenance of anaesthesia. It is too weak to be used alone, but it allows the dosage of other anaesthetic agents to be reduced. It has a strong analgesic action.

Oxygen should be added routinely during anaesthesia with inhalational agents, even when air is used as the carrier gas, to protect against hypoxia. Oxygen is also used in the management of anaphylaxis (section 3.1), myocardial infarction (section 12.5), and severe acute asthma (section 25.1).

Identification of cylinders for inhalation gases
An ISO standard (International Standard 32, Gas cylinders for medical use, 1977) requires that cylinders containing nitrous oxide should bear the name of the contents in legible and permanent characters and, preferably, also the chemical symbol N₂O. The neck, from the valve to the shoulder, should be coloured blue. Cylinders containing oxygen intended for medical use should bear the name of the contents in legible and permanent characters and, preferably, also the chemical symbol O₂. The neck, from the valve to the shoulder, should be coloured white. Cylinders containing nitrous oxide and oxygen mixtures should be similarly labelled, and the neck coloured white and blue.

NITROUS OXIDE
Inhalation gas

Uses:
Maintenance of anaesthesia in combination with other anaesthetic agents (halothane, ether, or ketamine) and muscle relaxants; analgesia for obstetric practice, for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness

Contraindications:
demonstrable collection of air in pleural, 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; pregnancy (Appendix 2); interactions: Appendix 1

Dosage:
Anaesthesia, Adult and Child nitrous oxide mixed with 25–30% oxygen
Analgesia, 50% nitrous oxide mixed with 50% oxygen

Adverse effects:
nausea and vomiting; after prolonged administration megaloblastic anaemia, depressed white cell formation; peripheral neuropathy
OXYGEN
Inhalation gas
Uses:
To maintain an adequate oxygen tension in inhalational anaesthesia
FIRE HAZARD. Avoid use of cautery when oxygen is used with ether; reducing valves on oxygen cylinders must not be greased (risk of explosion)
Precautions:
Interactions: Appendix 1
Dosage:
Concentration of oxygen in inspired anaesthetic gases should never be less than 21%
Adverse effects:
Concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion, exudation and atelectasis

1.2 Local anaesthetics

Drugs used for conduction anaesthesia (also termed local or regional anaesthesia) act by causing a reversible block to conduction along nerve fibres. Local anaesthetics are used very widely in dental practice, for brief and superficial interventions, for obstetric procedures, and for specialized techniques of regional anaesthesia calling for highly developed skills. Where patient cooperation is required the patient must be psychologically prepared to accept the proposed procedure. Facilities and equipment for resuscitation should be readily available at all times. Local anaesthetic injections should be given slowly in order to detect inadvertent intravascular injection.

LOCAL INFILTRATION

Many simple surgical procedures that neither involve the body cavities nor require muscle relaxation can be performed under local infiltration anaesthesia. Lower-segment caesarean section can also be performed under local infiltration anaesthesia. The local anaesthetic drug of choice is lidocaine 0.5% with or without epinephrine. No more than 4 mg/kg of plain lidocaine or 7 mg/kg of lidocaine with epinephrine should be administered on any one occasion. The addition of epinephrine (adrenaline) diminishes local blood flow, slows the rate of absorption of the local anaesthetic, and prolongs its effect. Care is necessary when using epinephrine for this purpose since, in excess, it may produce ischaemic necrosis. It should not be added to injections used in digits or appendages.

SURFACE ANAESTHESIA

Topical preparations of lidocaine are available and topical eye...
drop solutions of **tetracaine** (section 21.3) are used for local anaesthesia of the cornea and conjunctiva.

**REGIONAL BLOCK**
A regional nerve block can provide safe and effective anaesthesia but its execution requires considerable training and practice. Nevertheless, where the necessary skills are available, techniques such as axillary or ankle blocks can be invaluable. Either **lidocaine** 1% or **bupivacaine** 0.5% is suitable. Bupivacaine has the advantage of a longer duration of action.

**SPINAL ANAESTHESIA**
This is one of the most useful of all anaesthetic techniques and can be used widely for surgery of the abdomen and the lower limbs. It is a major procedure requiring considerable training and practice. Either **lidocaine** 5% in glucose or **bupivacaine** 0.5% in glucose can be used but the latter is often chosen because of its longer duration of action.

**BUPIVACAINE HYDROCHLORIDE**

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

*Injection* (Solution for injection), bupivacaine hydrochloride 2.5 mg/ml (0.25%), 10-ml ampoule; 5 mg/ml (0.5%), 10-ml ampoule; 5 mg/ml (0.5%) with glucose 75 mg/ml (7.5%), 4-ml ampoule

*Uses:*
Infiltration anaesthesia; peripheral and sympathetic nerve block; spinal anaesthesia; postoperative pain relief

*Contraindications:*
Adjacent skin infection, inflamed skin; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patient

*Precautions:*
Respiratory impairment; hepatic impairment (Appendix 5); epilepsy; porphyria; myasthenia gravis; pregnancy and breastfeeding (Appendices 2 and 3); *interactions:* Appendix 1

*Dosage:*
- Local infiltration, using 0.25% solution, **ADULT** up to 150 mg (up to 60 ml)
- Peripheral nerve block, using 0.5% solution, **ADULT** up to 150 mg (up to 30 ml)
- Dental anaesthesia, using 0.5% solution, **ADULT** 9–18 mg (1.8–3.6 ml)
- Lumbar epidural block in surgery, using 0.5% solution, **ADULT** 50–100 mg (10–20 ml)
- Lumbar epidural block in labour, using 0.25–0.5% solution, **ADULT** (female) up to 60 mg (maximum 12 ml)

Caudal block in surgery, using 0.25–0.5% solution, **ADULT** up to 150 mg (maximum 30 ml)
Caudal block in labour, using 0.25–0.5% solution, **ADULT** (female) up to 100 mg (maximum 20 ml)

**Note**

Maximum cumulative safe dose for adults and children of a 0.25% solution of bupivacaine is 1.5 mg/kg
Use lower doses for debilitated, elderly, epileptic, or acutely ill patients
Do not use solutions containing preservatives for spinal, epidural, caudal or intravenous regional anaesthesia

**Adverse effects:**

with excessive dosage or following intravascular injection, light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness and respiratory failure; cardiovascular toxicity includes hypotension, heart block and cardiac arrest; hypersensitivity and allergic reactions also occur; epidural anaesthesia occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation; transient paraesthesia and paraplegia very rare

**LIDOCAINE HYDROCHLORIDE**

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

**Injection** (Solution for injection), lidocaine hydrochloride 5 mg/ml (0.5%), 20-ml ampoule; 10 mg/ml (1%), 20-ml ampoule; 50 mg/ml (5%), 2-ml ampoule to be mixed with glucose 75 mg/ml (7.5%)

**Injection** (Solution for injection) with epinephrine, lidocaine hydrochloride 10 mg/ml (1%) with epinephrine 5 micrograms/ml (1 in 200 000), 20-ml ampoule

**Injection** (Solution for injection) with epinephrine (dental use), lidocaine hydrochloride 20 mg/ml (2%) with epinephrine 12.5 micrograms/ml (1 in 80 000), 2.2-ml dental cartridge

**Topical gel or solution**, lidocaine hydrochloride 20–40 mg/ml (2–4%)**

**Uses:**

Surface anaesthesia of mucous membranes; infiltration anaesthesia; peripheral and sympathetic nerve block; dental anaesthesia; spinal anaesthesia; intravenous regional anaesthesia; arrhythmias (section 12.2)

**Contraindications:**

Adjacent skin infection, inflamed skin; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patient

**Precautions:**

Respiratory impairment; hepatic impairment (Appendix 5); epilepsy; porphyria; myasthenia gravis; avoid (or use with

great care) solutions containing epinephrine (adrenaline) for ring block of digits or appendages (risk of ischaemic necrosis); pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

**Dosage:**

**Plain Solutions**

Local infiltration and peripheral nerve block, using 0.5% solution, **ADULT** up to 250 mg (up to 50 ml)

Local infiltration and peripheral nerve block, using 1% solution, **ADULT** up to 250 mg (up to 25 ml)

Surface anaesthesia of pharynx, larynx, trachea, using 4% solution, **ADULT** 40–200 mg (1–5 ml)

Surface anaesthesia of urethra, using 4% solution, **ADULT** 400 mg (10 ml)

Spinal anaesthesia, using 5% solution (with glucose 7.5%), **ADULT** 50–75 mg (1–1.5 ml)

**Solutions containing epinephrine**

Local infiltration and peripheral nerve block, using 0.5% solution with epinephrine, **ADULT** up to 400 mg (up to 80 ml)

Local infiltration and peripheral nerve block, using 1% solution with epinephrine, **ADULT** up to 400 mg (up to 40 ml)

Dental anaesthesia, using 2% solution with epinephrine, **ADULT** 20–100 mg (1–5 ml)

**NOTE.** Maximum safe doses of lidocaine for **adult** and **child** are: 0.5% or 1% lidocaine, 4 mg/kg; 0.5% or 1% lidocaine + epinephrine 5 micrograms/ml (1 in 200 000), 7 mg/kgUse lower doses for debilitated, elderly, epileptic, or acutely ill patientsDo not use solutions containing preservatives for spinal, epidural, caudal or intravenous regional anaesthesia

**Adverse effects:**

with excessive dosage or following intravascular injection, light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness and respiratory failure; cardiovascular toxicity includes hypotension, heart block and cardiac arrest; hypersensitivity and allergic reactions also occur; epidural anaesthesia occasionally complicated by urinary retention, faecal incontinence, headache, backache or loss of perineal sensation; transient paraesthesia and paraplegia very rare

Vasoconstrictors

The sympathetic block from spinal or epidural anaesthesia may cause hypotension. Such hypotension is managed by giving intravenous fluids (usually prophylactically) and oxygen, and elevating legs and giving a pressor drug such as ephedrine.

In addition to vasoconstriction, ephedrine also accelerates the heart rate and can therefore counter bradycardia (but atropine sulfate is used to reverse persistent bradycardia).
EPHEDRINE HYDROCHLORIDE

Ephedrine hydrochloride is a complementary drug
Injection (Solution for injection), ephedrine hydrochloride 30 mg/ml, 1-ml ampoule
Uses:
Prevention of hypotension during delivery under spinal or epidural anaesthesia
Precautions:
Hyperthyroidism; diabetes mellitus; ischaemic heart disease, hypertension; angle-closure glaucoma; renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1
Dosage:
To prevent hypotension during delivery under spinal anaesthesia, by slow intravenous injection of solution containing 3 mg/ml, ADULT (female) 3–6 mg (maximum single dose 9 mg), repeated if necessary every 3–4 minutes; maximum cumulative dose 30 mg
Adverse effects:
anorexia, hypersalivation, nausea, vomiting; tachycardia (also in fetus), arrhythmias, anginal pain, vasoconstriction with hypertension, vasodilation with hypotension; dyspnoea; headache, dizziness, anxiety, restlessness, confusion, tremor; difficulty in micturition; sweating, flushing; changes in blood-glucose concentration
EPINEPHRINE (ADRENALINE)
Uses:
Vasoconstrictor to retard systemic absorption of infiltrated local anaesthetics
Contraindications:
Ring block of digits, penis or other situations where there is risk of local ischaemia
Precautions:
Hypertension, atherosclerotic heart disease, cerebral vascular insufficiency, heart block; thyrotoxicosis or diabetes mellitus; interactions: Appendix 1
Dosage:
Final concentration 5 micrograms/ml (1 in 200 000); in dental surgery, in which small volumes are injected, concentrations of up to 12.5 micrograms/ml (1 in 80 000) commonly used; total dose should not exceed 500 micrograms

1.3 Preoperative medication and sedation

Pre-anaesthetic medication is often advisable prior to both conduction and general anaesthetic procedures. Sedatives improve the course of subsequent anaesthesia
in apprehensive patients. Diazepam and promethazine are effective. Diazepam can be administered by mouth, by rectum, or by intravenous injection. Promethazine, which has antihistaminic and antiemetic properties as well as a sedative effect, is of particular value in children.

Midazolam is a water soluble benzodiazepine which is often used in preference to intravenous diazepam; recovery is faster than from diazepam. Midazolam is associated with profound sedation when high doses are given intravenously or when used with certain other drugs.

A potent analgesic such as morphine (section 1.5) should be administered preoperatively to patients in severe pain or for analgesia during and after surgery.

Anticholinergic (more correctly antimuscarinic) drugs such as atropine are also used before general anaesthesia. They inhibit excessive bronchial and salivary secretions induced, in particular, by ether and ketamine. Intramuscular administration is most effective, but oral administration is more convenient in children. Lower doses should be used in cardiovascular disease or hyperthyroidism.

Chloral hydrate and derivatives were formerly popular hypnotics for children (but the use of hypnotics in children is not usually justified). There is no convincing evidence that they are particularly useful in the elderly and their role as hypnotics is now very limited.

**ATROPINE SULFATE**

*Injection (Solution for injection), atropine sulfate 600 micrograms/ml, 1-ml ampoule*

**Uses:**
To inhibit salivary secretions; to inhibit arrhythmias resulting from excessive vagal stimulation; to block the parasympathomimetic effects of anticholinesterases such as neostigmine; organophosphate poisoning (section 4.2.3); antispasmodic (section 17.5); mydriasis and cycloplegia (section 21.5)

**Contraindications:**
Angle-closure glaucoma; myasthenia gravis; paralytic ileus, pyloric stenosis; prostatic enlargement

**Precautions:**
Down syndrome, children, elderly; ulcerative colitis, diarrhoea; hyperthyroidism; heart failure, hypertension; pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

**Duration of action.** Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may
result; close monitoring of the patient is necessary

Dosage:
Premedication, by intramuscular injection 30–60 minutes before induction, ADULT and Child 20 micrograms/kg; by intravenous injection immediately before induction, ADULT up to maximum 500 micrograms
Inhibition of bradycardia, by intravenous injection, ADULT 0.4–1 mg, CHILD 10–30 micrograms/kg
Reversal of neuromuscular block, by intravenous injection 2–3 minutes before anticholinesterase, ADULT 0.6–1.2 mg, CHILD 20 micrograms/kg

Adverse effects:
Dry mouth; blurred vision, photophobia; flushing and dryness of skin, rash; difficulty in micturition; less commonly arrhythmias, tachycardia, palpitations; confusion (particularly in elderly); heat prostration and convulsions, especially in febrile children

DIAZEPAM
Drug subject to international control under the Convention on Psychotropic Substances (1971)
Diazepam is a representative benzodiazepine. Various drugs can serve as alternatives
Tablets, diazepam 2 mg, 5 mg
Injection (Solution for injection), diazepam 5 mg/ml, 2-ml ampoule

Uses:
Premedication before major or minor surgery; sedation with amnesia for endoscopic procedures and surgery under local anaesthesia; in combination with pethidine [not included on WHO Model List], when anaesthetic not available, for emergency reduction of fractures; epilepsy (section 5.1); anxiety disorders (section 24.3)

Contraindications:
central nervous system depression or coma; shock; respiratory depression; acute pulmonary insufficiency; sleep apnoea; acute alcohol intoxication; severe hepatic impairment; myasthenia gravis

Precautions:
Respiratory disease; muscle weakness; history of alcohol or drug abuse; marked personality disorder; elderly or debilitated patients (adverse effects more common in these groups); hepatic impairment (Appendix 5) or renal failure (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); porphyria; interactions: Appendix 1

Patient Advice. Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours

Dosage:
Premedication, by mouth 2 hours before surgery, ADULT and

CHILD over 12 years, 5–10 mg
Sedation, by slow intravenous injection immediately before procedure, ADULT and CHILD over 12 years, 200 micrograms/kg

ADMINISTRATION
Absorption following intramuscular injection 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.

Adverse effects:
central nervous system effects common and include drowsiness, sedation, confusion, amnesia, vertigo, and ataxia; hypotension, bradycardia, or cardiac arrest, particularly in elderly or severely ill patients; also paradoxical reactions, including irritability, excitability, hallucinations, sleep disturbances; pain and thromboembolism on intravenous injection.

PROMETHAZINE HYDROCHLORIDE

Tablets, promethazine hydrochloride 10 mg, 25 mg
Elixir (Oral solution), promethazine hydrochloride 5 mg/5 ml
Injection, (Solution for injection), promethazine hydrochloride 25 mg/ml, 2-ml ampoule

Uses:
Premedication prior to surgery; antiemetic (section 17.2)

Contraindications:
Child under 1 year; impaired consciousness due to cerebral depressants or of other origin; porphyria

Precautions:
Prostatic hypertrophy, urinary retention; glaucoma; epilepsy; hepatic impairment (Appendix 5); pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

Patient Advice
Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours.

Dosage:
Premedication, by mouth 1 hour before surgery, CHILD over 1 year 0.5–1 mg/kg
Premedication, by deep intramuscular injection 1 hour before surgery, ADULT 25 mg

Adverse effects:
Drowsiness (rarely paradoxical stimulation in children); headache; anticholinergic effects such as dry mouth, blurred vision, urinary retention

MIDAZOLAM

Injections, Midazolam: 1 mg/ml (5ml,)

Uses:
Preoperative sedation and provides conscious sedation prior to diagnostic or radiographic procedures; ICU sedation (continuous infusion); intravenous anesthesia (induction) intravenous anesthesia (maintenance)

Contraindications:
Hypersensitivity to midazolam or any component of the formulation including benzyl alcohol (cross sensitivity with other benzodiazepines may exist); narrow angle-glaucoma; pregnancy

Precautions:
May cause severe respiratory depression, respiratory arrest, and/or apnea. Use with caution in patients with respiratory disease. May cause hypotension-hemodynamic effects. Use with caution in obese patients, chronic renal failure and CHF. Midazolam causes anterograde amnesia. Paradoxical reactions, including hyperactive or aggressive behavior particularly in adolescent/pediatric or psychiatric patients.

Patient advice.
Warn patient not to perform skilled tasks, for example operating machinery, driving, for 24 hours

Dosage:

ADULT, preoperative sedation: I.M.: 0.07-0.08 mg/kg 30-60 minutes prior to surgery/procedure; usual dose: 5 mg; Note: Reduce dose in patients with COPD, high-risk patients, patients ≥60 years of age, and patients receiving other narcotics or CNS depressants I.V.: 0.02-0.04 mg/kg; repeat every 5 minutes as needed to desired effect or up to 0.1-0.2 mg/kg Intransal (not an approved route): 0.2 mg/kg (up to 0.4 mg/kg in some studies); administer 30-45 minutes prior to surgery/procedure

Conscious sedation: I.V.: Initial: 0.5-2 mg slow I.V. over at least 2 minutes; slowly titrate to effect by repeating doses every 2-3 minutes if needed; usual total dose: 2.5-5 mg; use decreased doses in elderly. Healthy Adults <60 years: Initial: Some patients respond to doses as low as 1 mg; no more than 2.5 mg should be administered over a period of 2 minutes. Additional doses of midazolam may be administered after a 2-minute waiting period and evaluation of sedation after each dose increment. A total dose >5 mg is generally not needed. If narcotics or other CNS depressants are administered concomitantly, the midazolam dose should be reduced by 30%. Refer to elderly dosing for patients 60 years, debilitated, or chronically ill. Maintenance: 25% of dose used to reach sedative effect

Adverse effects:
Drowsiness (rarely paradoxical stimulation in children); headache; anticholinergic effects such as dry mouth, blurred vision, urinary retention, respiratory depression, respiratory arrest

CHLORAL HYDRATE

Mixture, chloral hydrate 500 mg/5ml

Uses:
Insomnia (short-term use)

Contraindications:
Cardiac disease, gastritis, hepatic impairment, renal impairment, pregnancy and breast-feeding; porphyria

Precautions:
Respiratory disease, history of drug or alcohol abuse, marked personality disorder, reduce dose in elderly and delibitated; avoid prolonged use (and abrupt withdrawal thereafter); avoid contact with skin and mucuous membranes

Dosage:
Insomnia, 0.5-1 g (max. 2 g) with plenty of water at bedtime; CHILD 30-50 mg/kg up to max. single dose of 1 g

Adverse effects:
Gastric irritation (nausea and vomiting reported), abdominal distension and flatulence; also vertigo, ataxia, staggering gait, rashes, headache, light headedness, malaise, ketonuria, excitement, nightmares, delirium (especially in the elderly); eosinophilia, reduction in white cell count; dependence (may be associated with gestrititis and renal damage) on prolonged use

1.4 Muscle relaxants and cholinesterase inhibitors

Muscle relaxants used in surgery are classified according to their mode of action as 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.

Suxamethonium is the only widely used depolarizing muscle relaxant. It produces rapid, complete paralysis, which is very short-lasting in most patients and is of particular value for laryngoscopy and intubation. Should paralysis be prolonged, ventilation must be assisted until muscle function is fully restored. Suxamethonium normally produces a phase I (depolarizing) neuromuscular block. After high doses or prolonged use, the nature of the block changes to a phase II (non-depolarizing) block; this phase II block (also known as dual block) is associated with prolonged neuromuscular blockade and apnoea.

Atracurium is a non-depolarizing muscle relaxant with an intermediate duration of action. It undergoes non-enzyme metabolism which is independent of liver and kidney function, thus allowing its use in patients with hepatic or renal impair-
ment. Cardivascular effects are associated with significant histamine release. **Mivacurium**, another non-depolarizing muscle relaxant, has a short duration of action. It is metabolized by plasma cholinesterase and muscle paralysis in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release may occur, particularly with rapid injection. **Pancuronium** is a non-depolarizing muscle relaxant with a long duration of action and it is often used in patients receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

**REVERSAL OF BLOCK**

Cholinesterase inhibitors, such as **neostigmine** and **pyridostigmine**, are used at the end of an operation to reverse the muscle paralysis produced by non-depolarizing blocking drugs, such as atracurium, mivacurium and pancuronium. Neostigmine must not be used with depolarizing blocking drugs, such as suxamethonium, since neostigmine will prolong the muscle paralysis. Neostigmine is also used to treat postoperative non-obstructive urinary retention. For use of cholinesterase inhibitors in myasthenia gravis, see section 20.2.

**Muscle relaxants**

**ATRACURIUM BESILATE**

Atracurium is a representative non-depolarizing muscle relaxant. Various drugs can serve as alternatives

**Injection** (Solution for injection), atracurium chloride 10 mg/ml, 5-ml ampoule

**Uses:**

Muscle relaxation (short to intermediate duration) for surgery or during intensive care

**Contraindications:**

Respiratory insufficiency or pulmonary disease; dehydrated or severely ill patients; myasthenia gravis or other neuromuscular disorders

**Precautions:**

Renal or hepatic impairment possibly increase dose in patient with burns; electrolyte disturbances; possibly decrease dose in respiratory acidosis or hypokalemia; history of asthma; pregnancy and breastfeeding

**Dosage:**

Surgery or intubation, *by intravenous injection*, **ADULT** and **CHILD** over 1 month initially 300–600 micrograms/kg, maintenance, by intravenous injection, 100-200 micrograms/ kg as
required or by intravenous infusion, 5-10 micrograms/kg/minute (300-600 micrograms/kg/hour) Intensive care, ADULT and CHILD over 1 month, by intravenous injection, initially 300-600 micrograms/kg (optional) then by intravenous infusion 4.5-29.5 micrograms/kg/minute (usual dose 11-13 micrograms/kg/minute)

Adverse effects:
Histamine release, causing allergic reactions, such as wheal and flare effects at site of injection, flushing, bronchospasm (anaphylactoid reactions reported); transient hypotension, slight increase in heart rate or decreased pulse rate

MIVACURIUM (SAD)
Mivacurium is a short acting non-depolarizing muscle relaxant
Injection (Powder for solution for injection), mivacurium chloride, 10-mg vial
Uses:
Muscle relaxation (short duration) for surgery
Contraindications:
Respiratory insufficiency or pulmonary disease; dehydrated or severely ill patients; myasthenia gravis or other neuromuscular disorders
Precautions:
Renal impairment, hepatic impairment; possibly increase dose in patient with burns; electrolyte disturbances; possibly decrease dose in respiratory acidosis or hypokalemia; history of asthma; severe obesity (maintenance of adequate airway and ventilation support); pregnancy and breastfeeding
Dosage:
Intubation, by intravenous injection, 70-250 micrograms/kg; maintenance 100 micrograms/kg every 15 minutes; CHILD 2-6 months initially 150 micrograms/kg, 7 months-12 years initially 200 micrograms/kg; maintenance (CHILD 2 months – 12 years) 100 micrograms/kg every 6-9 minutes.
NOTE. Doses up to 150 micrograms/kg may be given over 5-15 seconds, higher doses should be given over 30 seconds. In patients with asthma, cardiovascular disease or those who are sensitive to falls in arterial blood pressure give over 60 seconds
By intravenous infusion, maintenance of block, 8-10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose of 6-7 micrograms/kg/minute; CHILD 2 months-12 years usual dose 11-14 micrograms/kg/minute
Adverse effects:
Minimal release of histamine (rarely hypersensitivity reactions including bronchospasm, hypotension, tachycardia, oedema, erythema, pruritus)
PANCURONIUM

Injection, 2 mg/ml; 2ml
Uses:
Non-depolarizing muscle relaxant of longer duration
Contraindications:
Severe renal impairment
Precautions:
Patients to whom tachycardia is hazardous, also, patients with myasthenia gravis, hypermagnesemia, hypokalemia, hypocalcemia, respiratory insufficiency, suppressed hepatic or renal function, elderly patients, and neonates.
Dosage:
By intravenous injection, initially for intubation 50-100 micrograms/kg then 10-20 micrograms/kg as required; CHILD initially 60-100 micrograms/kg, then 10-20 micrograms/kg; NEONATE 30-40 micrograms/kg initially then 10-20 micrograms/kg
Intensive care; by intravenous injection, 60 micrograms/kg every 60-90 minutes
Adverse effects:
Histamine release, causing allergic reactions, such as wheal and flare effects at site of injection, flushing, bronchospasm (anaphylactoid reactions reported); transient hypotension, slight increase in heart rate or decreased pulse rate

SUXXAMETHONIUM CHLORIDE

Injection (Solution for injection), suxamethonium chloride 50 mg/ml, 2-ml ampoule
Injection (Powder for solution for injection), suxamethonium chloride
Note.
Powder formulation recommended; liquid requires refrigerated storage
Uses:
Brief muscular paralysis during endotracheal intubation, endoscopy and electroconvulsive therapy
Contraindications:
Inability to maintain clear airway; personal or family history of malignant hyperthermia; neurological disease involving acute wasting of major muscle, prolonged immobilization (risk of hyperkalaemia); personal or family history of congenital myotonic disease; Duchenne muscular dystrophy; myasthenia gravis; glaucoma, ocular surgery; liver disease; burns; low plasma cholinesterase activity (including severe liver disease); hyperkalaemia
Precautions:
Digitalis toxicity or recent digitalization; cardiac, respiratory
or neuromuscular disease; paraplegia, spinal cord injury, or severe trauma; severe sepsis (risk of hyperkalaemia); prolonged apnoea on repeated injection (infusion preferred for long surgical procedures); hepatic impairment (Appendix 5); renal impairment; pregnancy (Appendix 2); children; interactions: Appendix 1

Dosage:
Muscle relaxation, by intramuscular injection, INFANT up to 4–5 mg/kg; CHILD up to 4 mg/kg; maximum 150 mg
Muscle relaxation, by intravenous injection, ADULT and CHILD 1 mg/kg, followed if necessary by supplements of 0.5–1 mg/kg at 5–10 minute intervals; INFANT 2 mg/kg
Muscle relaxation (prolonged procedures), by intravenous infusion, ADULT 2.5–4 mg/minute of solution containing 1–2 mg/ml; maximum 500 mg/hour; child reduce infusion rate according to body weight

Adverse effects:
Postoperative muscle pain, particularly in patients ambulant after operation, and more common in females; myoglobinuria; myoglobinaemia; prolonged apnoea; increased intra-ocular pressure; hyperkalaemia; bradycardia, hypotension, arrhythmias, particularly with halothane (however, with repeated doses tachycardia, hypertension); increased saliva, bronchial and gastric secretions; transient rise in intragastric pressure; hypersensitivity reactions including flushing, rash, urticaria, bronchospasm, and shock (more common in women, in history of allergy, or in asthmatics); rarely, malignant hyperthermia (often fatal)

Cholinesterase inhibitor

Neostigmine metilsulfate

Injection (Solution for injection), neostigmine metilsulfate 500 micrograms/ml, 1-ml ampoule; 2.5 mg/ml, 1-ml ampoule

Uses:
Counteract effect of non-depolarizing muscle relaxants administered during surgery; postoperative non-obstructive urinary retention; myasthenia gravis (section 20.2)

Contraindications:
Recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis

Precautions:
Asthma; urinary tract infections; cardiovascular disease, including arrhythmias (especially bradycardia or atrioventricular block); vagotonia; hypotension; peptic ulcer; epilepsy; Parkinsonism; hyperthyroidism; avoid before halothane administration has been stopped; maintain adequate ventilation (respiratory
1.4 Muscle relaxants and cholinesterase inhibitors

acidosis predisposes to arrhythmias); renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

**Dosage:**
Reversal of non-depolarizing block, *by intravenous injection* over 1 minute, **ADULT** 2.5 mg, followed if necessary by supplements of 500 micrograms to maximum total dose of 5 mg; **CHILD** 40 micrograms/kg (titrated using peripheral nerve stimulator)

**Note.**
To reduce muscarinic effects atropine sulfate *by intravenous injection* (**ADULT** 0.6–1.2 mg, **CHILD** 20 micrograms/kg) with or before neostigmine

Postoperative urinary retention, *by subcutaneous or intramuscular injection*, **ADULT** 500 micrograms (catheterization required if urine not passed within 1 hour)

**Adverse effects:**
Increased salivation and bronchial secretions, nausea and vomiting, abdominal cramps, diarrhoea; allergic reactions, hypotension

**PYRIDOSTIGMINE**
Tablet, 60 mg,

**Uses:**
Myasthenia gravis and reversal of non-depolarizing Neuromuscular blocking agents

**Contraindications:**
See under neostigmine

**Precautions:**
See under neostigmine

**Dosage:**
**ADULT:**
Initially 60mg orally three times daily increasing gradually to lowest possible maintenance dose (usually 600mg daily)

**PAED:**
7mg/kg/24 hours divided into 5-6 doses

**Adverse effects:**
Increased salivation and bronchial secretions, nausea and vomiting, abdominal cramps, diarrhoea; allergic reactions, hypotension

**OTHER MUSCLE RELAXANTS**

**ORPHENADRINE HYDROCHLORIDE**
Tablet, orphenadrine hydrochloride 100 mg

**Uses:**
Short-term symptomatic relief of muscle spasm

**Contraindications:**
Avoid use in children, Patients with glaucoma, cardiospasm, and GI obstruction.

**Precautions:**
Reduce doses in the elderly and patients with CHF.

**Dosage:**
Oral - 100mg each morning and evening

**Adverse effects:**
Dizziness, drowsiness, dry mouth, constipation, pruritus

**DANTROLENE**

*Injection, 20 mg*

**Uses:**
Malignant hyperthermia, muscle spasm in spastic conditions

**Contraindications:**
Active liver disease e.g. hepatitis, cirrhosis

**Precautions:**
Liver dysfunction, pulmonary or cardiac impairment. Female patients over 35 years especially on estrogen. Do not give to nursing mothers

**Dosage:**
Malignant hyperthermia - rapid I.V. injection, 1mg/kg, repeated as required to a cumulative maximum of 10mg/kg

**Adverse effects:**
Transient drowsiness, diarrhoea, muscle weakness, fatigue

### 1.5 Analgesics and opioid antagonists

Opioid analgesics, such as morphine, may be used to supplement general anaesthesia, usually in combination with nitrous oxide–oxygen and a muscle relaxant. Repeated doses of intra-operative analgesics should be given with care, since respiratory depression may persist into the postoperative period.

The specific opioid antagonist naloxone will immediately reverse this respiratory depression but the dose may need to be repeated. Other resuscitative measures must also be available. It is important to remember that naloxone will also antagonize the analgesic effect of opioids.

Non-opioid drugs, paracetamol, aspirin and nonsteroidal anti-inflammatory drugs may be useful alternatives (or adjuncts) for the relief of postoperative pain; they do not affect respiration and gastrointestinal motility. They are particularly suitable for pain in musculoskeletal conditions.

Aspirin is indicated for headaches, transient musculoskeletal pain, dysmenorrhea and pyrexia.

Paracetamol is similar in efficacy to aspirin, but have no demonstrable anti-inflammatory activity.

Nonsteroidal anti inflammatory analgesics NSAIDs are
particularly helpful for the treatment of patients with chronic disease accompanied by pain and inflammation.

**Opioid analgesics**

Opioid analgesics are usually to relieve moderate to severe pain particularly if visceral origin. Repeat administration may cause dependence and tolerance. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain. **Morphine** remains the most valuable opioid analgesic for severe pain although if frequently causes nausea and vomiting. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment. **Codeine** is effective for the relief of mild to moderate pain but is too constipating for long term use.

**Morphine**

Drug subject to international control under the Single Convention on Narcotic Drugs (1961) **Injection** (Solution for injection), morphine (as hydrochloride or sulfate) 10 mg/ml, 1-ml ampoule

**Uses:**
Adjunct during major surgery; postoperative analgesia; pain, myocardial infarction, acute pulmonary oedema (section 2.2)

**Contraindications:**
acute respiratory depression; increased intracranial pressure, head injury or brain tumour; severe hepatic impairment (Appendix 5); adrenocortical insufficiency; hypothyroidism; convulsive disorders; acute alcoholism, delirium tremens; diverticulitis and other spastic conditions of colon; recent surgery on biliary tract; diarrhoea due to toxins

**Precautions:**
Asthma, emphysema, or heart failure secondary to chronic lung disease; ability to maintain airway; if used in biliary colic, antispasmodic needed; renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3); **overdose:** section 4.2.2; **interactions:** Appendix 1

**Dosage:**
Premedication, **by subcutaneous or intramuscular injection** 1 hour before surgery, **ADULT** 150–200 micrograms/kg; **by intramuscular injection** 1 hour before surgery, **CHILD** 50–100 micrograms/kg

Intra-operative analgesia, **by intravenous injection**, **ADULT** and **CHILD** 100 micrograms/kg, repeated every 40–60 minutes as required

Postoperative analgesia, **by intramuscular injection**, **ADULT** 150–300 micrograms/kg every 4 hours, **CHILD** 100–200 micrograms/kg; or **by intravenous infusion** **ADULT** 8–10 mg over
30 minutes, then 2–2.5 mg/hour

**Adverse effects:**
respiratory depression; anorexia, nausea, vomiting, constipation; euphoria, dizziness, drowsiness, confusion, headache; dry mouth; spasm of urinary and biliary tract; circulatory depression, hypotension, bradycardia, palpitations; miosis; allergic reactions; physical dependence

**Opioid antagonists**

**NALOXONE HYDROCHLORIDE**

*Injection* (Solution for injection), naxolone hydrochloride 400 micrograms/ml, 1-ml ampoule

**Uses:**
To counteract respiratory depression induced by opioids during anaesthesia; opioid overdosage (see also section 4.2.2)

**Precautions:**
Dependence on opioids; cardiovascular disease

**Dosage:**
Opioid-induced respiratory depression, *by intravenous injection*, **ADULT** 100–200 micrograms, repeated every 2–3 minutes to obtain required response; **CHILD** initially 10 micrograms/kg, if no response followed by 100 micrograms/kg

Opioid-induced respiratory depression at birth, *by subcutaneous, intramuscular, or intravenous injection*, **NEONATE** 10 micrograms/kg immediately after delivery

**Adverse effects:**
Nausea and vomiting; hypertension and hypotension reported; left ventricular failure; pulmonary oedema; seizures; arrhythmias such as ventricular tachycardia or fibrillation, particularly in pre-existing cardiac disease

1.6 **Blood substitutes and solutions for correcting fluid imbalance**

Fluid requirements must be assessed before, during and after major surgery. Replacement fluids should correspond as nearly as possible in volume and composition to those lost. Blood transfusion is essential to restore oxygen-carrying capacity when more than 15% of the circulating blood volume is lost but should be avoided whenever screening for human immunodeficiency viruses and hepatitis B virus is impracticable. Isotonic sodium chloride solution may be used for short-term volume replacement. Plasma expanders such as dextran 70 or polygeline may be useful. Provided renal function is maintained, fluid is most simply replaced by intravenous administration of **sodium chloride solution** (sodium chloride 9 mg/ml, 0.9%) or the more physiologically appropriate **compound solution**
of sodium lactate. In emergency cases, there is usually an existing fluid deficit, which must be assessed and corrected before surgery. Isotonic glucose/sodium chloride mixtures (most commonly glucose 4%/sodium chloride 0.18%) are preferred in children to avoid the danger of sodium overload and hypoglycaemia. When fluids are administered intravenously for more than 24 hours, potassium chloride is required to prevent potassium depletion. In order to avoid serious arrhythmias, especially in patients with impaired renal function, the required dose of potassium should be determined, whenever possible, by monitoring plasma concentrations of potassium. See also sections 11.1 (plasma substitutes) and 26.2 (solutions correcting water, electrolyte, and acid-base disturbances).
1.6 Blood substitutes and solutions for correcting fluid imbalance
Section 2: Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, drugs used to treat gout, and disease-modifying antirheumatic drugs

2.1 Non-opoid analgesic
   2.1.1 Acetylsalicylic acid,
   2.1.2 Paracetamol
   2.1.3 NSAID
2.2 Opioid analgesic
2.3 Medicines used to treat gout
   2.3.1 Acute gout
   2.3.2 Chronic gout
2.4 Disease modifying agents used in rheumatoid disorder (DMARDS)
Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, drugs used to treat gout, and disease-modifying antirheumatic drugs

Pain can be classified as acute or chronic. Acute pain is usually of short duration and the cause often identifiable (disease, trauma). Chronic pain persists after healing is expected to be complete, or is caused by a chronic disease. Pain may be modified by psychological factors and attention to these is essential in pain management. Drug treatment aims to modify the peripheral and central mechanisms involved in the development of pain. Neurogenic pain generally responds poorly to conventional analgesics; treatment can be difficult and includes the use of carbamazepine (section 5.1) for trigeminal neuralgia and amitriptyline (section 24.2.1) for diabetic neuropathy and postherpetic neuralgia.

Non-opioid analgesics (section 2.1) are particularly suitable for pain in musculoskeletal conditions whereas the opioid analgesics (section 2.2) are more suitable for moderate to severe visceral pain. Those non-opioid analgesics which also have anti-inflammatory actions include salicylates and NSAIDs (nonsteroidal anti-inflammatory drugs); they can reduce both pain and inflammation of chronic inflammatory disorders such as rheumatoid arthritis, but they do not alter or modify the disease process itself. For the management of rheumatoid arthritis DMARDs (disease-modifying antirheumatic drugs) may favourably influence the outcome of the disease (section 2.4). The pain and inflammation of an acute attack of gout is treated with a NSAID or colchicine (section 2.3.1); a xanthine-oxidase inhibitor (section 2.3.2) is used for long-term control of gout.

2.1 Non-opioid analgesics

Non-opioid analgesics with anti-inflammatory activity include salicylates such as acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs such as ibuprofen. Non-opioid analgesics with little or no anti-inflammatory activity include paracetamol.

2.1.1 Acetylsalicylic acid

The principal effects of acetylsalicylic acid are anti-inflammatory, analgesic, antipyretic and antiplatelet. Oral doses are absorbed rapidly from the gastrointestinal tract; rectal absorption is less reliable but suppositories are useful in patients unable to take oral dosage forms. Acetylsalicylic acid is used for the management of mild to moderate pain such as headache, acute migraine attacks (section 7.1), transient musculoskeletal pain and dysmenorrhoea, and for reducing fever. Although it may be used in higher doses in the management of pain and inflam-
mation of rheumatoid arthritis, other NSAIDs are preferred because they are likely to be better tolerated. Acetylsalicylic acid is also used for its antiplatelet properties (section 12.5). Adverse effects with analgesic doses are generally mild but include a high incidence of gastrointestinal irritation with slight blood loss, bronchospasm and skin reactions in hypersensitive patients, and increased bleeding time. Anti-inflammatory doses are associated with a much higher incidence of adverse reactions, and they also cause mild chronic salicylism which is characterized by tinnitus and deafness. Acetylsalicylic acid should be avoided in children under 16 years, unless specifically indicated (for example juvenile arthritis), because of an association with Reye syndrome (encephalopathy and liver damage); it should particularly be avoided during fever or viral infection in children and adolescents.

Acetylsalicylic acid

Tablets, acetylsalicylic acid 300 mg, 81mg Dispersible tablets (Soluble tablets), acetylsalicylic acid 300 mg [not included on the WHO Model List] Uses: Mild to moderate pain including dysmenorrhoea, headache; pain and inflammation in rheumatic disease and other musculoskeletal disorders (including juvenile arthritis); pyrexia; acute migraine attack (section 7.1); antiplatelet (section 12.5); maybe used as prophylaxis of myocardial infarction

Contraindications: Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (Reye syndrome—see also notes above); gastrointestinal ulceration; haemophilia and other bleeding disorders; not for treatment of gout

Precautions: Asthma, allergic disease; impaired renal or hepatic function (Appendices 4 and 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; G6PD-deficiency; dehydration; interactions: Appendix 1

Dosage: Mild to moderate pain, pyrexia, by mouth with or after food, ADULT 300–900 mg every 4–6 hours if necessary; maximum 4 g daily; CHILD under 16 years not recommended Mild to moderate pain, pyrexia, by rectum, ADULT 600–900 mg inserted every 4 hours if necessary; maximum 3.6 g daily; CHILD under 16 years not recommended Inflammatory arthritis, by mouth with or after food, ADULT 4–8 g daily in divided doses in acute conditions; up to 5.4 g daily may be sufficient in chronic conditions Juvenile arthritis, by mouth with or after food, 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
Myocardial Infarction prophylaxis: 75mg-325mg/day, use of lower aspirin dose has been recommended in patients receiving ACE inhibitors

**Adverse effects:**
Generally mild and infrequent for lower doses, but common with anti-inflammatory doses; gastrointestinal discomfort or nausea, ulceration with occult bleeding (occasionally major haemorrhage); also other haemorrhage (including subconjunctival); hearing disturbances such as tinnitus (rarely deafness), vertigo, confusion, hypersensitivity reactions (angioedema, bronchospasm and rash); increased bleeding time; rarely oedema, myocarditis, blood disorders (particularly thrombocytopenia)

**Paracetamol**
*Paracetamol* is similar in analgesic and antipyretic efficacy to acetylsalicylic acid. It is used for mild to moderate pain including headache and acute migraine attacks (section 7.1) and for reducing fever, including post-immunization pyrexia. Paracetamol is particularly useful in patients in whom salicylates or other NSAIDs are contraindicated, such as asthmatics and those with a history of peptic ulcer, or for children under the age of 16 years in whom salicylates should be avoided because of the risk of Reye syndrome. It is generally preferred to acetylsalicylic acid, particularly in the elderly, because it is less irritating to the stomach. Unlike acetylsalicylic acid and other NSAIDs, paracetamol has little anti-inflammatory activity which limits its usefulness for long-term treatment of pain associated with inflammation; however it is useful in the management of osteoarthritis, a condition with only a small inflammatory component. In normal doses adverse effects are rare, but overdosage with a single dose of 10–15 g is particularly dangerous because it may cause hepatocellular necrosis and, less frequently, renal tubular necrosis.

**Paracetamol**
*Tablets*, paracetamol 500 mg;  
*Dispersible tablets (Soluble tablets)*, paracetamol 120 mg, 500 mg [not included on WHO Model List]  
*Oral solution*, paracetamol 120 mg/5 ml, 125 mg/5 ml, 250 mg/5 ml [120 mg/5 ml and 250 mg/5 ml strengths not included on WHO Model List]  
*Suppositories*, paracetamol 60 mg, 100 mg, 125 mg, 250 mg, 500 mg [only 100-mg strength included on WHO Model List]

**Uses:**
Mild to moderate pain including dysmenorrhoea, headache;
pain relief in osteoarthritis and soft tissue lesions; pyrexia including post-immunization pyrexia; acute migraine attack (section 7.1)

**Precautions:**
Hepatic impairment (Appendix 5); renal impairment; alcohol dependence; breastfeeding (Appendix 3); **overdosage**: section 4.2.1; **interactions**: Appendix 1

**Dosage:**
Post-immunization pyrexia, by mouth, **INFANT** 2–3 months, 60 mg followed by a second dose, if necessary, 4–6 hours later; warn parents to seek medical advice if pyrexia persists after second dose
Mild to moderate pain, pyrexia, by mouth, **ADULT** 0.5–1 g every 4–6 hours, maximum 4 g daily; **CHILD** under 3 months see note below, 3 months–1 year 60–125 mg, 1–5 years 120–250 mg, 6–12 years 250–500 mg, these doses may be repeated every 4–6 hours if necessary (maximum 4 doses in 24 hours)
Mild to moderate pain, pyrexia, by rectum, **ADULT** 0.5–1 g;
**CHILD** 1–5 years 125–250 mg, 6–12 years 250–500 mg; doses inserted every 4–6 hours if necessary, maximum 4 doses in 24 hours

**Note.**
Infants under 3 months should not be given paracetamol unless advised by a doctor; a dose of 10 mg/kg (5 mg/kg if jaundiced) is suitable

**Adverse effects:**
Rare but rashes and blood disorders reported; **important:** liver damage (and less frequently renal damage) following overdosage

2.1.3 **NSAIDs (nonsteroidal anti-inflammatory drugs)**

NSAIDs, including **ibuprofen**, have analgesic, anti-inflammatory and antipyretic properties. In single doses NSAIDs have analgesic activity comparable to that of paracetamol. In regular full dosage, they have a lasting analgesic and anti-inflammatory effect, which makes them useful for continuous or regular pain due to inflammation. Differences in anti-inflammatory activity between different NSAIDs are small but there is considerable variation in individual patient response and in the incidence and type of adverse effects. Ibuprofen has fewer adverse effects than other NSAIDs but its anti-inflammatory properties are weaker. Diclofenac and naproxen (neither of which is included on the WHO Model List) combine moderately potent anti-inflammatory activity with a relatively low incidence of adverse effects (but incidence is higher than that for ibuprofen).

Ibuprofen is used in the treatment of mild to moderate pain and in the management of pain and inflammation in rheumatoid arthritis and juvenile arthritis. It may also be of value in
the less well-defined conditions of back pain and soft-tissue disorders. Ibuprofen is also used to reduce pain in children. With all NSAIDs caution should be exercised in the treatment of the elderly, in allergic disorders, during pregnancy and breastfeeding. In patients with renal, cardiac or hepatic impairment, the dose should be kept as low as possible and renal function should be monitored. NSAIDs should not be given to patients with active peptic ulceration and should preferably not be used in those with a history of the disease. The commonest adverse effects are generally gastrointestinal including nausea, vomiting, diarrhoea, and dyspepsia; hypersensitivity reactions including anaphylaxis, bronchospasm, and rash have been reported, as has fluid retention. *Naproxen* is another propionic acid derivative with actions similar to ibuprofen, with a low incidence of side-effects. *Diclofenac* have actions similar to that of naproxen; their side-effects are also similar to naproxen. *Indomethacin* has action to or superior to that of naproxen, but with high incidence of side effects. *Piroxicam* is as effective as naproxen and has a prolong duration of action which permits once daily administration. It has more gastrointestinal side-effects than ibuprofen, especially in the elderly.

**IBUPROFEN**

*Tablets*, Ibuprofen 200 mg, 400 mg

*Syrup*, 100mg/5ml

**Uses:**

Pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis; mild to moderate pain including dysmenorrhoea, headache; pain in children; acute migraine attack (section 7.1)

**Contraindications:**

Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration

**Precautions:**

Renal and hepatic impairment (Appendices 4 and 5); preferably avoid if history of peptic ulceration; cardiac disease; elderly; pregnancy and breastfeeding (Appendices 2 and 3); coagulation defects; allergic disorders; **interactions**: Appendix 1

**Dosage:**

Mild to moderate pain, pyrexia, inflammatory musculoskeletal disorders, *by mouth* with or after food, **ADULT** 1.2–1.8 g daily in 3–4 divided doses, increased if necessary to maximum 2.4 g daily (3.2 g daily in inflammatory disease); maintenance dose of 0.6–1.2 g daily may be sufficient
Juvenile arthritis, *by mouth* with or after food, **CHILD** over 7 kg, 30–40 mg/kg daily in 3–4 divided doses

Pain in children (not recommended for child under 7 kg), *by mouth* with or after food, 20–40 mg/kg daily in divided doses or 1–2 years 50 mg 3–4 times daily, 3–7 years 100 mg 3–4 times daily, 8–12 years 200 mg 3–4 times daily

**Adverse effects:**
Gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastrointestinal haemorrhage; hypersensitivity reactions including rash, angioedema, bronchospasm; headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity, haematuria; fluid retention (rarely precipitating congestive heart failure in elderly), raised blood pressure, renal failure; rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic dermal necrolysis (Lyell syndrome), colitis, aseptic meningitis

**NAPROXEN**
*Tablets*, 250mg, 500mg

**Uses:**
Management of inflammatory disease and rheumatoid disorders; gout; mild to moderate pain; dysmenorrhea; fever, migraine headache

**Precautions:**
Use with caution in patients with GI disease, cardiovascular disease, dehydration, renal or hepatic impairment and patients receiving anticoagulants. As many as 60% of elderly can develop peptic ulceration and/or haemorrhaging asymptotically use with caution.

**Contraindications:**
Hypersensitivity to naproxen, aspirin, other NSAIDs, or any component of the formulation; pregnancy in the (3rd trimester)

**Dosage:**
ADULTS: Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis: 500-1000mg mg/day in 2 divided dose; may increase to 1.5 g/day
Mild to moderate pain dysmenorrhea: Initiate: 500mg, then 250mg every 6-8hrs, maximum: 1250mg/day

**Adverse effects:**
Headache, nervousness, malaise, pruritus, rash, heartburn, constipation, dyspepsia, perforation, indigestion, diarrhea, heart burn, tinnitus
Rare but rashes and blood disorders reported; **important:** liver damage (and less frequently renal damage) following overdosage

**Patient advice.**

Avoid alcohol; take naproxen with food

**DICLOFENAC**

*Tablets, 50mg*

*Injection iv/im, 25mg/ml/3ml*

**Use**
Immediate release: Ankylosing spondylitis; primary dysmenorrhea; acute and chronic treatment of rheumatoid arthritis, osteoarthritis

**Contraindications**
Hypersensitivity to diclofenac, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass surgery; pregnancy (3rd trimester)

**Precautions**
- Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Use caution with fluid retention, CHF, or hypertension. Gastrointestinal events NSAIDs may increase risk of gastrointestinal irritation, ulceration, bleeding, and perforation. Use with caution in patients with decreased hepatic function. Use of NSAIDs can compromise existing renal function.

**Adverse Reactions**
Headache, dizziness, pruritus, rash, fluid retention, abdominal cramps, abdominal pain, constipation, diarrhea, flatulence, indigestion, nausea, abdominal distention, peptic ulcer/GI bleed

**Dosage**
- **ADULTS**, analgesia/primary dysmenorrhea: Starting dose: 50 mg 3 times/day; maximum dose: 150 mg/day
- Rheumatoid arthritis: 150-200 mg/day in 2-4 divided doses (100 mg/day of sustained release product)
- Osteoarthritis: 100-150 mg/day in 2-3 divided doses (100-200 mg/day of sustained release product)
- Ankylosing spondylitis: 100-125 mg/day in 4-5 divided doses

**INDOMETHACIN**

*Tablet, 25mg*

*Suppository, 100mg*

**Use**
Acute gouty arthritis, acute bursitis/tendonitis, moderate to severe osteoarthritis, rheumatoid arthritis, ankylosing spondylitis; I.V. form used as alternative to surgery for closure of patent ductus arteriosus in neonates
Contraindications
Hypersensitivity to indomethacin, or any component of the formulation; pregnancy (3rd trimester)
Neonates: Necrotizing enterocolitis, impaired renal function, active bleeding, thrombocytopenia, coagulation defects, untreated infection

Precautions
Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, CHF, or hypertension. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use caution with epilepsy; use may aggravate this condition. Use with caution in patients with decreased hepatic function and existing renal function.

Adverse Reactions
Headache, fatigue, vertigo, depression, malaise, somnolence, nausea, epigastric pain, abdominal pain/cramps/distress, heartburn, indigestion, constipation, diarrhea, dyspepsia, vomiting

Dosage
Patent ductus arteriosus:
Neonates: I.V.: Initial: 0.2 mg/kg, followed by 2 doses depending on postnatal age (PNA):
PNA at time of first dose <48 hours: 0.1 mg/kg at 12- to 24-hour intervals
PNA at time of first dose 2-7 days: 0.2 mg/kg at 12- to 24-hour intervals
PNA at time of first dose >7 days: 0.25 mg/kg at 12- to 24-hour intervals
In general, may use 12-hour dosing interval if urine output >1 mL/kg/hour after prior dose; use 24-hour dosing interval if urine output is <1 mL/kg/hour but >0.6 mL/kg/hour; doses should be withheld if patient has oliguria (urine output <0.6 mL/kg/hour) or anuria
Inflammatory/rheumatoid disorders: Oral: Use lowest effective dose.
Children e2 years: 1-2 mg/kg/day in 2-4 divided doses; maximum dose: 4 mg/kg/day; not to exceed 150-200 mg/day
Adults: 25-50 mg/dose 2-3 times/day; maximum dose: 200 mg/day. In patients with arthritis and persistent night pain and/or morning stiffness may give the larger portion (up to 100 mg) of the total daily dose at bedtime.
Bursitis/tendonitis: Oral: Adults: Initial dose: 75-150 mg/day in 3-4 divided doses; usual treatment is 7-14 days

Acute gouty arthritis: Oral: Adults: 50 mg 3 times daily until pain is tolerable then reduce dose; usual treatment <3-5 days
Elderly: Refer to adult dosing. Use lowest recommended dose and frequency in elderly to initiate therapy for indications listed in adult dosing.

**PIROXICAM**

Capsule, 20mg
Use
Symptomatic treatment of acute and chronic rheumatoid arthritis and osteoarthritis

**Precautions**
Use with caution in patients with impaired cardiac function, dehydration, hypertension, impaired renal function, GI disease and patients receiving anticoagulants.

**Adverse Reactions**
Dizziness, edema, rash, gastrointestinal, abdominal cramps, heartburn, indigestion, nausea, headache, nervousness, itching, fluid retention, vomiting, tinnitus

**Dosage,**
**ADULTS:** 10-20 mg/day once daily; although associated with increase in GI adverse effects, doses >20 mg/day have been used (ie, 30-40 mg/day)

### 2.2 Opioid analgesics

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.

**Morphine** remains the most valuable analgesic for severe pain. In addition to pain relief it confers a state of euphoria and mental detachment; repeated administration may cause dependence and tolerance, but this should not be a deterrent in the control of pain in terminal illness (see also section 8.4). Regular use may also be appropriate for certain cases of non-malignant pain, but specialist supervision is required. In normal doses common adverse effects include nausea, vomiting, constipation and drowsiness; larger doses produce respiratory depression and hypotension.

**Codeine** is an opioid analgesic much less potent than morphine and much less liable, in normal doses, to produce adverse effects including dependency. It is effective for mild to moderate pain but is too constipating for long-term use.

**Methadone** is less sedating than morphine and acts for longer periods. Methadone may be used instead of morphine in the oc-
casional patient who experiences excitation with morphine.

**Oxycodone** has an efficacy and side-effect profile similar to that of morphine. It is used primarily for control of pain in palliative care.

**Pethidine** produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high dose is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesic in labour.

**Fentanyl** is used by injection for intra-operative analgesia.

**CODEINE PHOSPHATE**

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

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

*Tablets*, codeine phosphate, 30 mg,

**Uses:**
Mild to moderate pain; diarrhoea (section 17.7.2)

**Contraindications:**
Respiratory depression, obstructive airways disease, acute asthma attack; where risk of paralytic ileus

**Precautions:**
Renal and hepatic impairment (Appendices 4 and 5); dependence; pregnancy (Appendix 2); breastfeeding (Appendix 3); **overdose:** section 4.2.2; **interactions:** Appendix 1

**Dosage:**
Mild to moderate pain, *by mouth*, **ADULT** 30–60 mg every 4 hours when necessary to a maximum of 240 mg daily; **CHILD** 1–12 years, 0.5–1 mg/kg every 4–6 hours when needed

**Adverse effects:**
Constipation particularly troublesome in long-term use; dizziness, nausea, vomiting; difficulty with micturition; ureteric or biliary spasm; dry mouth, headaches, sweating, facial flushing; in therapeutic doses, codeine is much less liable than morphine to produce tolerance, dependence, euphoria, sedation or other adverse effects

**MORPHINE SALTS**

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

Tablets, morphine sulfate 10 mg

Oral solution, morphine hydrochloride or sulfate 10 mg/5 ml

Injection (Solution for injection), morphine sulfate 10 mg/ml, 1-ml ampoule

Uses:
Severe pain (acute and chronic); myocardial infarction, acute pulmonary oedema; adjunct during major surgery and postoperative analgesia (section 1.5)

Contraindications:
Acute respiratory depression, acute alcoholism, where risk of paralytic ileus; raised intracranial pressure or head injury (interferes with respiration, also affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma

Precautions:
Renal and hepatic impairment (Appendices 4 and 5); reduce dose or avoid in elderly and debilitated; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; pregnancy (Appendix 2) and breastfeeding (Appendix 3); overdose: section 4.2.2; interactions: Appendix 1

Dosage:
Acute pain, by subcutaneous injection (not suitable for oedematous patients) or by intramuscular injection ADULT 10 mg every 4 hours if necessary (15 mg for heavier well-muscled patients); INFANT up to 1 month 150 micrograms/kg, 1–12 months 200 micrograms/kg; CHILD 1–5 years 2.5–5 mg, 6–12 years 5–10 mg

Chronic pain, by mouth or by subcutaneous injection (not suitable for oedematous patients) or by intramuscular injection 5–20 mg regularly every 4 hours; dose may be increased according to need; oral dose should be approximately double corresponding intramuscular dose

Myocardial infarction, by slow intravenous injection (2 mg/minute), 10 mg followed by a further 5–10 mg if necessary; elderly or debilitated patients, reduce dose by half

Acute pulmonary oedema, by slow intravenous injection (2 mg/minute), 5–10 mg

Note.
The doses stated above refer equally to morphine sulfate and hydrochloride

Adverse effects:
Nausea, vomiting (particularly in initial stages) constipation;
drowsiness; also dry mouth, anorexia, spasm of urinary and biliary tract; bradycardia, tachycardia, palpitations, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, dependence, miosis; larger doses produce respiratory depression and hypotension

**Acetaminophen/Codeine**

*Tablets, 300mg/30mg*

**Use**
Relief of moderate to moderately-severe pain

**Precaution**
Use with caution in patients with hypersensitivity to other phenanthrene derivative opioid agonists; respiratory disease including asthma, emphysema, COPD, or severe liver or renal insufficiency

**Contraindications**
Opioid-dependent patients; acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids, or psychotropic drugs

**Adverse Reactions**
Flushing, dizziness, headache, insomnia, somnolence, pruritus, constipation, nausea, vomiting, dyspepsia

**Dosage**
Moderate-to-severe chronic pain, **ADULTS**, Analgesic based on codeine (30-60mg) every 4-6hrs (maximum 360mg/24 hours based on codeine component)

**HYDROMORPHONE**

*Tablets, 4mg, tablet CR 3mg*

**Use**
Management of moderate-to-severe pain

**Contraindications**
Hypersensitivity to hydromorphone, any component of the formulation; acute or severe asthma, severe respiratory depression (in absence of resuscitative equipment or ventilatory support); severe CNS depression; pregnancy (prolonged use or high doses at term); obstetrical analgesia

**Precautions**
May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness, may cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics), myoclonus and seizures have been reported with

high doses, use with caution in patients with hepatic impairment, use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages; use with caution in patients with thyroid dysfunction

Contraindications
Acute or severe asthma, severe respiratory depression (in absence of resuscitative equipment or ventilatory support); severe CNS depression; pregnancy (prolonged use or high doses at term); obstetrical analgesia

Dosage
Acute pain (moderate to severe), CHILDREN >50 kg and ADULTS, oral, initial: Opiate-naive: 2-4 mg every 3-6 hours as needed; elderly/debilitated patients may require lower doses; patients with prior opiate exposure may require higher initial doses; usual dosage range: 2-8 mg every 3-4 hours as needed

OXYCODONE

Tablet Cr, 20mg, IR 10mg

Use
Management of moderate-to-severe pain, normally used in combination with nonopioid analgesics. Treatment of postoperative pain

Contraindications
Significant respiratory depression; hypercarbia; acute or severe bronchial asthma; Oxycondone is also contraindicated in paralytic ileus (known or suspected); pregnancy (prolonged use or high doses at term)

Precautions
May cause CNS depression use with caution . May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics). Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (codeine, hydrocodone, hydromorphone, oxymorphone).

Adverse Reactions
Somnolence, dizziness, pruritus, nausea, constipation , vomiting, abnormal dreams, anxiety, chills, confusion , euphoria, fever, insomnia, nervousness, thought abnormalities, rash

Dosage
Oral, ADULTS, immediate release: 5 mg every 6 hours as needed, max 400mg daily
METHADONE

Powder, 1mg/ml

Use
Management of moderate-to-severe pain; detoxification and maintenance treatment of opioid addiction (if used for detoxification and maintenance treatment of narcotic addiction, it must be part of an FDA-approved program)

Contraindications
Hypersensitivity to methadone or any component of the formulation; respiratory depression (in the absence of re-suscitative equipment or in an unmonitored setting); acute bronchial asthma or hypercarbia; paralytic ileus; concurrent use of selegiline

Precautions
May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Adverse Reactions
Bradycardia, peripheral vasodilation, cardiac arrest, syncope, faintness, shock, hypotension, edema, arrhythmia, bigeminal rhythms, extrasystoles, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia, ECG changes, QT interval prolonged, T-wave inversion, cardiomyopathy, flushing, heart failure, palpitation, phlebitis, orthostatic hypotension, euphoria, dysphoria, hallucination, headache, insomnia, agitation, disorientation, drowsiness, dizziness, lightheadedness, sedation, confusion, seizure, pruritus, urticaria, rash, hemorrhagic urticaria, libido decreased, hypokalemia, hypomagnesemia, antidiuretic effect, amenorrhea, nausea, vomiting, constipation, anorexia, stomach cramps, xerostomia, biliary tract spasms, abdominal pain, glossitis, weight gain, urinary retention or hesitancy, impotence, thrombocytopenia, weakness

Dosage
Analgesia, oral: initial: 0.1-0.2 mg/kg 4-8 hours initially for 2-3 doses, then every 6-12 hours as needed. Dosing interval may range from 4-12 hours during initial therapy; decrease in dose or frequency may be required (days 2-5) due to accumulation with repeated doses (maximum dose: 5-10 mg)

I.V.: 0.1 mg/kg every 4-8 hours initially for 2-3 doses, then every 6-12 hours as needed. Dosing interval may range from 4-12 hours during initial therapy; decrease in dose or frequency may be required (days 2-5) due to accumulation with repeated doses
Iatrogenic narcotic dependency: Oral: General guidelines: Initial: 0.05-0.1 mg/kg/dose every 6 hours; increase by 0.05 mg/kg/dose until withdrawal symptoms are controlled; after 24-48 hours, the dosing interval can be lengthened to every 12-24 hours; to taper dose, wean by 0.05 mg/kg/day; if withdrawal symptoms recur, taper at a slower rate.

ADULTS:
Acute pain (moderate-to-severe):
Oral: Opioid-naive: Initial: 2.5-10 mg every 8-12 hours; more frequent administration may be required during initiation to maintain adequate analgesia. Dosage interval may range from 4-12 hours, since duration of analgesia is relatively short during the first days of therapy, but increases substantially with continued administration.

Chronic pain (opioid-tolerant): Conversion from oral morphine to oral methadone:
Daily oral morphine dose <100 mg: Estimated daily oral methadone dose: 20% to 30% of total daily morphine dose
Daily oral morphine dose 100-300 mg: Estimated daily oral methadone dose: 10% to 20% of total daily morphine dose
Daily oral morphine dose 300-600 mg: Estimated daily oral methadone dose: 8% to 12% of total daily morphine dose
Daily oral morphine dose 600-1000 mg: Estimated daily oral methadone dose: 5% to 10% of total daily morphine dose.
Daily oral morphine dose >1000 mg: Estimated daily oral methadone dose: <5% of total daily morphine dose.

PETHIDINE

Injection, 50mg/ml, 100mg/ml

Tablet, 50mg

Use
Management of moderate-to-severe pain; adjunct to anesthesia and preoperative sedation, adjunct in preoperative intravenous conscious sedation in patients undergoing dental surgery; alternate oral narcotic in patients allergic to codeine to treat moderate to moderate-severe pain

Contraindications
Hypersensitivity to meperidine or any component of the formulation; use with or within 14 days of MAO inhibitors; pregnancy (prolonged use or high doses near term)

Precautions
May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness. Normeperidine (an active metabolite and CNS stimulant) may accumulate and precipitate anxiety, tremors, or seizures; risk increases with
renal dysfunction and cumulative dose. May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

**Adverse Reaction**

Hypotension, fatigue, drowsiness, dizziness, nervousness, headache, restlessness, malaise, confusion, mental depression, hallucinations, paradoxical CNS stimulation, increased intracranial pressure, seizure, serotonin syndrome

**Dosage**

**CHILDREN**: Pain: Oral, I.M., I.V., SubQ: 1-1.5 mg/kg/dose every 3-4 hours as needed; 1-2 mg/kg as a single dose preoperative medication may be used; maximum 100 mg/dose (Note: Oral route is not recommended for acute pain.)

**ADULTS**: Pain: Oral: Initial: Opiate-naive: 50 mg every 3-4 hours as needed; usual dosage range: 50-150 mg every 2-4 hours as needed (manufacturers recommendation; oral route is not recommended for acute pain)

I.M., SubQ: Initial: Opiate-naive: 50-75 mg every 3-4 hours as needed; patients with prior opiate exposure may require higher initial doses

Preoperatively: 50-100 mg given 30-90 minutes before the beginning of anesthesia

**FENTANYL**

*Injection as the citrate, 50mcg/ml/2ml*

**Use**

Injection: Sedation, relief of pain, preoperative medication, adjunct to general or regional anesthesia

**Contraindications**

Hypersensitivity to fentanyl or any component of the formulation; increased intracranial pressure; severe respiratory disease or depression including acute asthma (unless patient is mechanically ventilated); paralytic ileus; severe liver or renal insufficiency; pregnancy (prolonged use or high doses near term)

**Precautions**

Abuse/misuse/diversion: [U.S. Boxed Warning]: Healthcare provider should be alert to problems of abuse, misuse, and diversion.

Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

**Adverse Reactions**

Hypotension, bradycardia, CNS depression, confusion, drowsiness, sedation, nausea, vomiting, constipation, xerostomia,
weakness, miosis, respiratory depression, diaphoresis

Dosage

Sedation for minor procedures/analgesia:

CHILDREN 1-12 years:
Sedation for minor procedures/analgesia: I.M., I.V.: 1-2 mcg/kg/dose; may repeat at 30- to 60-minute intervals. Note: Children 18-36 months of age may require 2-3 mcg/kg/dose
Continuous sedation/analgesia: Initial I.V. bolus: 1-2 mcg/kg; then 1-3 mcg/kg/hour to a maximum dose of 5 mcg/kg/hour
CHILDREN >12 YEARS and ADULTS: I.V.: 25-50 mcg; may repeat every 3-5 minutes to desired effect or adverse event; maximum dose of 500 mcg/4 hours; higher doses are used for major procedures

Surgery: ADULTS:
Premedication: I.M., slow I.V.: 25-100 mcg/dose 30-60 minutes prior to surgery
Adjunct to regional anesthesia: Slow I.V.: 25-100 mcg/dose over 1-2 minutes. Note: An I.V. should be in place with regional anesthesia so the I.M. route is rarely used but still maintained as an option in the package labeling.
Adjunct to general anesthesia: Slow I.V.: Low dose: 0.5-2 mcg/kg/dose depending on the indication. For example, 0.5 mcg/kg will provide analgesia or reduce the amount of propofol needed for laryngeal mask airway insertion with minimal respiratory depression. However, to blunt the hemodynamic response to intubation 2 mcg/kg is often necessary.
Moderate dose: Initial: 2-15 mcg/kg/dose; Maintenance (bolus or infusion): 1-2 mcg/kg/hour. Discontinuing fentanyl infusion 30-60 minutes prior to the end of surgery will usually allow adequate ventilation upon emergence from anesthesia. For “fast-tracking” and early extubation following major surgery, total fentanyl doses are limited to 10-15 mcg/kg.
High dose: Note: High-dose (20-50 mcg/kg/dose) fentanyl is rarely used, but is still maintained in the package labeling.

Acute pain management: ADULTS:
Severe: I.M, I.V.: 50-100 mcg/dose every 1-2 hours as needed; patients with prior opiate exposure may tolerate higher initial doses
Patient-controlled analgesia (PCA): I.V.: Usual concentration: 10 mcg/mL
Demand dose: Usual: 10 mcg; range: 10-50 mcg
Lockout interval: 5-8 minutes
Mechanically-ventilated patients (based on 70 kg patient): Slow I.V.: 0.35-1.5 mcg/kg every 30-60 minutes as needed; infusion: 0.7-10 mcg/kg/hour

Breakthrough cancer pain: For patients who are tolerant to and currently receiving opioid therapy for persistent cancer
pain; dosing should be individually titrated to provide adequate analgesia with minimal side effects. Dose titration should be done if patient requires more than 1 dose/breakthrough pain episode for several consecutive episodes. Patients experiencing >4 breakthrough pain episodes/day should have the dose of their long-term opioid re-evaluated.

Children ≤16 years and Adults: Lozenge: Initial dose: 200 mcg; the second dose may be started 15 minutes after completion of the first dose. Consumption should be limited to ≤4 units/day.

Adults: Buccal tablet (Fentora™): Initial dose: 100 mcg; a second 100 mcg dose, if needed, may be started 30 minutes after the start of the first dose. Note: For patients previously using the transmucosal lozenge (Actiq®), the initial dose should be selected using the conversions listed below (maximum: 2 doses per breakthrough pain episode every 4 hours). Dose titration, if required, should be done using multiples of the 100 mcg tablets. Patient can take two 100 mcg tablets (one on each side of mouth). If that dose is not successful, can use four 100 mcg tablets (two on each side of mouth). If titration requires >400 mcg/dose, then use 200 mcg tablets.

2.3 Drugs used in gout

Acute gout

Acute attacks of gout are usually treated with high doses of a NSAID such as indomethacin (150–200 mg daily in divided doses); ibuprofen has weaker anti-inflammatory properties than other NSAIDs and is therefore less suitable for treatment of gout. Salicylates, including acetylsalicylic acid are also not suitable because they may increase plasma-urate concentrations. Colchicine is an alternative for those patients in whom NSAIDs are contraindicated. Its use is limited by toxicity with high doses. It does not induce fluid retention and can therefore be given to patients with heart failure; it can also be given to patients receiving anticoagulants.

2.4 Chronic gout

For long-term control of gout in patients who have frequent attacks, the xanthine oxidase inhibitor allopurinol may be used to reduce production of uric acid. It should not be used to treat an acute attack since it may prolong it indefinitely. Treatment for chronic gout should not be started until after an acute attack has completely subsided, usually 2–3 weeks. The initiation of allopurinol treatment may precipitate an acute attack therefore colchicine or a suitable NSAID should be used as a prophylactic and continued for at least one month after the hyperuricaemia has been corrected. If an acute attack develops during treat-
ment for chronic gout, then allopurinol should continue at the same dosage and the acute attack should be treated in its own right. Treatment for chronic gout must be continued indefinitely to prevent further attacks of gout.

**ALLOPURINOL**

*Tablets*, allopurinol 100 mg, 300 mg

**Uses:**
Prophylaxis of gout; prophylaxis of hyperuricaemia associated with cancer chemotherapy

**Contraindications:**
Acute gout; if an acute attack occurs while receiving allopurinol, continue prophylaxis and treat attack separately

**Precautions:**
Ensure adequate fluid intake of 2–3 litres daily; pregnancy and breastfeeding (Appendices 2 and 3); renal and hepatic impairment (Appendices 4 and 5); withdraw treatment if rash occurs, reintroduce if rash is mild but discontinue immediately if it recurs; **interactions**: Appendix 1

**Dosage:**
Prophylaxis of gout, *by mouth*, **ADULT** initially 100 mg daily as a single dose, preferably after food, then adjusted according to plasma or urinary uric acid concentration; usual maintenance dose in mild conditions 100–200 mg daily, in moderately severe conditions 300–600 mg daily, in severe conditions 700–900 mg daily; doses over 300 mg daily given in divided doses

**Note.** Initiate 2–3 weeks after acute attack has subsided and administer colchicine or a suitable NSAID (*not* ibuprofen or a salicylate) from the start of allopurinol treatment and continue for at least 1 month after hyperuricaemia corrected

Prophylaxis of hyperuricaemia, *by mouth*, **ADULT** maintenance doses as for acute gout, adjusted according to response, started 24 hours before cancer treatment and continued for 7–10 days afterwards; **CHILD** under 15 years 10–20 mg/kg daily (maximum 400 mg daily)

**Adverse effects:**
Rash (see Precautions above), hypersensitivity reactions occur rarely and include fever, lymphadenopathy, arthralgia, eosinophilia, erythema multiforme (Stevens-Johnson syndrome) or toxic epidermal necrolysis, vasculitis, hepatitis, renal impairment and, very rarely, seizures; gastrointestinal disorders; rarely malaise, headache, vertigo, drowsiness, visual and taste disturbance, hypertension, alopecia, hepatotoxicity, paraesthesia, neuropathy, gynaecomastia, blood disorders (including leukopenia, thrombocytopenia, haemolytic anaemia and aplastic anaemia)

DMARDs (disease-modifying antirheumatic drugs)
The process of cartilage and bone destruction which occurs
in rheumatoid arthritis may be reduced by the use of a diverse group of drugs known as DMARDs (disease-modifying anti-rheumatic drugs). DMARDs include antimalarials (chloroquine, hydroxychloroquine), penicillamine, sulfasalazine, immunosuppressants (azathioprine, cyclophosphamide, methotrexate) and gold compounds. Treatment should be started early in the course of the disease, before joint damage starts. Treatment is usually initiated with a NSAID when the diagnosis is uncertain and the disease course unpredictable. However, when the diagnosis, progression and severity of rheumatic disease have been confirmed, a DMARD should be introduced.

DMARDs do not produce an immediate improvement but require 4–6 months of treatment for a full response. Their long-term use is limited by toxicity and loss of efficacy. If one drug does not lead to objective benefit within 6 months, it should be discontinued and another DMARD substituted. Adverse reactions with DMARDs occur frequently and may be life threatening; careful monitoring is needed to avoid severe toxicity. Blood disorders (bone marrow suppression) can occur during treatment with many DMARDs; blood counts should be carried out before and during treatment, and patients should be advised to report without delay any unexplained symptom such as bleeding, bruising, purpura, infection, sore throat or fever. It has been suggested that combinations of DMARDs may be more effective than single drugs but increased toxicity may be a problem; whether used alone or in combination, they should be prescribed only by specialists to ensure that they are used safely and to best advantage.

The antimalarial chloroquine is less effective than most other DMARDs, but as it is generally better tolerated it may be preferred in the treatment of mild rheumatoid arthritis. Chloroquine should not be used for psoriatic arthritis. Because long-term therapy can result in retinopathy ophthalmological examinations should be conducted before and during treatment.

Sulfasalazine has a beneficial anti-inflammatory effect and is considered by some rheumatologists to be a first-line DMARD, but it is poorly tolerated by about 25% of patients. Adverse reactions include blood disorders (bone marrow suppression), hepatotoxicity, skin reactions and gastrointestinal disturbances.

Methotrexate, an immunosuppressant, is considered to be a first-line DMARD; at the low doses used for rheumatoid arthritis it is well tolerated but there remains the risk of blood disorders (bone marrow suppression) and of hepatic and pulmonary toxicity. Other immunosuppressant drugs, including azathioprine, are generally reserved for use in patients with severe disease who have failed to respond to other DMARDs, especially in those with extra-cellular manifestations such as...
vasculitis. Immunosuppressants are used in psoriatic arthritis. Adverse reactions include blood disorders, alopecia, nausea and vomiting. **Penicillamine** is not a first-line drug and its use is limited by a significant incidence of adverse effects including blood disorders (bone marrow suppression), proteinuria and rash. **Corticosteroids** (section 18.1) are potent anti-inflammatory drugs but their place in the treatment of rheumatoid arthritis remains controversial. Their usefulness is limited by adverse effects and their use should be controlled by specialists. Corticosteroids are usually reserved for use in patients with severe disease which has failed to respond to other antirheumatic drugs, or where there are severe extra-articular effects such as vasculitis. Corticosteroids are also used to control disease activity during initial therapy with DMARDs. Although corticosteroids are associated with bone loss this appears to be dose-related; recent studies have suggested that a low dose of a corticosteroid started during the first two years of moderate to severe rheumatoid arthritis may reduce the rate of joint destruction. The smallest effective dose should be used, such as oral prednisolone 7.5 mg daily for 2–4 years only, and at the end of treatment the dose should be tapered off slowly to avoid possible long term adverse effects. Relatively high doses of a corticosteroid, with cyclophosphamide, may be needed to control vasculitis.

**AZATHIOPRINE**

Azathioprine is a complementary drug for rheumatoid arthritis. **Tablets**, azathioprine 50 mg  
**Uses:** Rheumatoid arthritis in cases that have failed to respond to chloroquine or penicillamine; psoriatic arthritis; transplant rejection (section 8.1); inflammatory bowel disease (section 17.4)  
**Contraindications:** Hypersensitivity to azathioprine or mercaptopurine  
**Precautions:** Monitor throughout treatment including blood counts; hepatic impairment (Appendix 5); renal impairment (Appendix 4); elderly (reduce dose); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1  
**Bone Marrow Suppression.** Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, purpura, infection, sore throat  
**Dosage:** Administered on expert advice
Rheumatoid arthritis, *by mouth*, initially, 1.5–2.5 mg/kg daily in divided doses, adjusted according to response; maintenance 1–3 mg/kg daily; consider withdrawal if no improvement within 3 months

**Adverse effects:**

Hypersensitivity reactions requiring immediate and permanent withdrawal include malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis; dose-related bone marrow suppression; liver impairment, cholestatic jaundice; hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis and pneumonitis. Hepatic veno-occlusive disease; also herpes zoster infection

**CHLOROQUINE SALTS**

*Tablets*, chloroquine sulfate 200 mg; chloroquine phosphate 250 mg

**Note.** Chloroquine base 150 mg is approximately equivalent to chloroquine sulfate 200 mg or chloroquine phosphate 250 mg

**Uses:**

Rheumatoid arthritis (including juvenile arthritis); malaria (section 6.4.3)

**Contraindications:**

Psoriatic arthritis

**Precautions:**

Monitor visual acuity throughout treatment; warn patient to report immediately any unexplained visual disturbances; hepatic impairment; renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); neurological disorders including epilepsy; severe gastrointestinal disorders; G6PD deficiency; elderly; may exacerbate psoriasis and aggravate myasthenia gravis; porphyria; **interactions:** Appendix 1

**Dosage:**

Administered on expert advice

**Note.** All doses in terms of chloroquine base

Rheumatoid arthritis, *by mouth*, **ADULT** 150 mg daily; maximum 2.5 mg/kg daily; **CHILD** up to 3 mg/kg daily

**Note.** To avoid excessive dosage in obese patients the dose of chloroquine should be calculated on the basis of lean body weight

**Adverse effects:**

Gastrointestinal disturbances, headache, skin reactions (rash, pruritus); less frequently ECG changes, convulsions, visual changes, retinal damage, keratopathy, ototoxicity, hair depigmentation, alopecia, discolouration of skin, nails and mucous membranes; rarely blood disorders (including thrombocytopenia, agranulocytosis, aplastic anaemia); mental changes
(including emotional disturbances, psychosis), myopathy (including cardiomyopathy and neuromyopathy), acute general-
ized exanthematous pustulosis, exfoliative dermatitis, erythema multiforme (Stevens-Johnson syndrome) and hepatic damage; 
important: arrhythmias and convulsions in overdosage

METHOTREXATE

Methotrexate is a complementary drug for rheumatoid arthritis
Tablets, methotrexate 2.5 mg

Uses: rheumatoid arthritis which has failed to respond to penicillamine or chloroquine; malignant disease (section 8.2)

Contraindications:
Pregnancy and breastfeeding (Appendices 2 and 3); immunodeficiency syndromes; significant pleural effusion or ascites

Precautions:
monitor throughout treatment including blood counts and hepatic and renal function tests; renal and hepatic impairment (avoid if severe, see also Appendices 4 and 5); reduce dose or withdraw if acute infection develops; for woman or man, contraception during and for at least 6 months after treatment; peptic ulceration, ulcerative colitis, diarrhoea, ulcerative stomatitis; advise patient to avoid self-medication with salicylates or other NSAIDs; warn patient with rheumatoid arthritis to report cough or dyspnoea; interactions: Appendix 1

Bone marrow suppression. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, purpura, infection, sore throat

Dosage:
Administered on expert advice
Rheumatoid arthritis, by mouth, ADULT 7.5 mg once weekly (as a single dose or divided into 3 doses of 2.5 mg given at intervals of 12 hours), adjusted according to response; maximum total dose of 15 mg (occasionally 20 mg) once weekly

IMPORTANT: The doses are weekly doses and care is required to ensure that the correct dose is prescribed and dispensed

Adverse effects:
Blood disorders (bone marrow suppression), liver damage, pulmonary toxicity; gastrointestinal disturbances—if stomatitis and diarrhoea occur, stop treatment; renal failure, skin reactions, alopecia, osteoporosis, arthralgia, myalgia, ocular irritation, precipitation of diabetes

PENICILLAMINE

Penicillamine is a complementary drug for rheumatoid arthritis

Capsules, penicillamine 125 mg, 250 mg [125-mg strength not included on WHO Model List]

Tablets, penicillamine 125 mg, 250 mg [125-mg strength not included on WHO Model List]

Uses:
Severe rheumatoid arthritis; copper and lead poisoning (section 4.2.5)

Contraindications:
Hypersensitivity; lupus erythematosus

Precautions:
Monitor throughout treatment including blood counts and urine tests; renal impairment (Appendix 4); pregnancy (Appendix 2); avoid concurrent gold, chloroquine or immunosuppressive treatment; avoid oral iron within 2 hours of a dose; interactions: Appendix 1

Bone marrow suppression. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, purpura, infection, sore throat

Dosage:
Administered on expert advice

Rheumatoid arthritis, by mouth, ADULT initially 125–250 mg daily before food for 1 month, increased by similar amounts at intervals of not less than 4 weeks to usual maintenance of 500–750 mg daily in divided doses; maximum 1.5 g daily; ELDERLY initially up to 125 mg daily before food for 1 month increased at intervals of not less than 4 weeks; maximum 1 g daily; CHILD 8–12 years initially 2.5–5 mg/kg daily, gradually increased to usual maintenance of 15–20 mg/kg daily at intervals of 4 weeks over a period of 3–6 months

Adverse effects:
Initially nausea (less of a problem if taken before food or on retiring, and if initial dose is only gradually increased), anorexia, fever; taste loss (mineral supplements not recommended); blood disorders including thrombocytopenia, neutropenia, agranulocytosis and aplastic anaemia; proteinuria, rarely haematuria (withdraw immediately); haemolytic anaemia, nephrotic syndrome, lupus erythematosus-like syndrome, myasthenia-like syndrome, polymyositis (rarely with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alo-
pecia, bronchiolitis and pneumonitis, pemphigus, glomerulonephritis (Goodpasture syndrome) and erythema multiforme (Stevens-Johnson syndrome) also reported; male and female breast enlargement reported; rash (early rash disappears on withdrawing treatment—reintroduce at lower dose and increase gradually; late rash is more resistant—either reduce dose or withdraw treatment)

**Sulfasalazine**

Sulfasalazine is a complementary drug for rheumatoid arthritis

*Enteric-coated tablets* (Gastro-resistant tablets), sulfasalazine 500 mg

**Uses:**
Severe rheumatoid arthritis; ulcerative colitis and Crohn disease (section 17.4)

**Contraindications:**
Hypersensitivity to salicylates and sulfonamides; severe renal impairment; child under 2 years; porphyria

**Precautions:**
monitor during first 3 months of treatment including blood counts and hepatic and renal function tests; renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); history of allergy; G6PD deficiency; slow acetylator status; interactions: Appendix 1

*Bone marrow suppression.* Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, purpura, infection, sore throat

**Dosage:**
Administered on expert advice

Rheumatoid arthritis, *by mouth* as gastro-resistant tablets, **ADULT** initially 500 mg daily, increased by 500 mg at intervals of 1 week to a maximum of 2–3 g daily in divided doses

**Adverse effects:**
Nausea, diarrhoea, headache, loss of appetite; fever; blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, thrombocytopenia); hypersensitivity reactions (including rash, urticaria, erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, lupus erythematosus-like syndrome); lung complications (including eosinophilia, fibrosing
alveolitis); ocular complications (including periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, hallucinations; kidney reactions (including proteinuria, crystalluria, haematuria); oligospermia; rarely acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained
Section 3: Antiallergics and drugs used in anaphylaxis

3.1 Antiallergics and drugs used in anaphylaxis
3.1 Antiallergics and drugs used in anaphylaxis

Antiallergics and drugs used in anaphylaxis

The H₁-receptor antagonists are generally referred to as antihistamines. They inhibit the wheal, pruritus, sneezing and nasal secretion responses that characterize allergy. Antihistamines thus relieve the symptoms of allergic reactions, such as urticaria, allergic rhinitis, and allergic conjunctivitis; they also control pruritus in skin disorders, such as eczema. Antihistamines are used to treat drug allergies, food allergies, insect stings and some of the symptoms of anaphylaxis and angioedema. Drug treatment and other supportive care should not be delayed in critically ill patients (see Allergic Emergencies below). Specific precipitants should be sought and if identified, further exposure avoided and desensitization considered.

Drowsiness and sedation are particular disadvantages of the older antihistamines and the patient should be warned against driving or operating machinery.

Non-sedating antihistamine such as Cetirizine and Loratidine cause less sedation and psychomotor impairment than older antihistamine because they penetrate the blood brain barrier to a slighter extent.

Antihistamine differ in their duration of action and incidence of drowsiness and antimuscarinic effects. Many older antihistamine are relatively short acting but some (promethazine) act up to 12 hours, while most of the newer non-sedating antihistamine are long acting.

Other central nervous depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics and neuroleptics, may enhance the sedative effects of antihistamines. Since antihistamines interfere with skin tests for allergy, they should be stopped at least one week before conducting a skin test.

Chlorpheniramine is a typical, older sedative antihistamine. Newer antihistamines do not cause significant sedation. In practice, all antihistamines are equally effective in relieving the symptoms of allergic reactions and differ mainly in the intensity of sedative and anticholinergic (more correctly antimuscarinic) effects. Selection of an antihistamine should thus be based on the intended therapeutic use, the adverse reaction profile, and the cost.

Corticosteroids, such as Dexamethasone, Hydrocortisone,

or Prednisolone, suppress or prevent almost all symptoms of inflammation associated with allergy. The route of administration depends on the particular type of allergic condition. For example, for a mild allergic skin reaction, the best therapy may be the use of a corticosteroid ointment or cream. If the skin reaction does not respond to topical corticosteroid therapy, it may be necessary to give a corticosteroid orally.

Allergic reactions of limited duration and with mild symptoms, such as urticaria or allergic rhinitis, usually require no treatment. If on the other hand, symptoms become persistent, antihistamines constitute the mainstay of treatment. However, oral corticosteroids may be required for a few days in an acute attack of urticaria or for severe skin reactions. Oral corticosteroids are also used to relieve severe exacerbations in chronic urticaria, but long-term use should be avoided.

Corticosteroids may be used topically to reduce inflammation in allergic rhinitis but should only be used systemically for this condition when symptoms are disabling.

Adverse effects associated with long-term use of corticosteroids include inhibition of growth in children, disturbances of electrolyte balance leading to oedema, hypertension and hypokalaemia, with osteoporosis, spontaneous fractures, skin thinning, increased susceptibility to infection, mental disturbances and diabetes mellitus.

Allergic emergencies

Anaphylactic shock and conditions such as angioedema are medical emergencies that can result in cardiovascular collapse and/or death. They require prompt treatment of possible laryngeal oedema, bronchospasm or hypotension. Atopic individuals are particularly susceptible. Insect stings and certain foods including eggs, fish, cow’s milk protein, peanuts and nuts are a risk for sensitized persons. Therapeutic substances particularly associated with anaphylaxis include blood products, vaccines, hyposensitizing (allergen) preparations, antibiotics (especially penicillins), iron injections, heparin, and neuromuscular blocking drugs. Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) may cause bronchoconstriction in leukotriene-sensitive patients. In the case of drug allergy, anaphylaxis is more likely to occur after parenteral administration. Resuscitation facilities should always be available when injecting a drug associated with a risk of anaphylactic reactions.

First-line treatment of a severe allergic reaction includes administering epinephrine (adrenaline), keeping the airway open.
(with assisted respiration if necessary), and restoring blood pressure (laying the patient flat, raising the feet). Epinephrine (adrenaline) should immediately be given by intramuscular injection to produce vasoconstriction and bronchodilation and injection should be repeated if necessary at 5-minute intervals until blood pressure, pulse and respiratory function have stabilized. If there is cardiovascular shock with inadequate circulation, epinephrine (adrenaline) must be given cautiously by slow intravenous injection of a dilute solution. Oxygen administration is also of primary importance.

An antihistamine such as chlorpheniramine is a useful adjunctive treatment given after epinephrine (adrenaline) injection and continued for 24 to 48 hours to reduce the severity and duration of symptoms and to prevent relapse. An intravenous corticosteroid such as hydrocortisone has an onset of action that is delayed by several hours but should be given to help prevent later deterioration in severely affected patients.

Further treatment of anaphylaxis may include intravenous fluids, an intravenous vasopressor such as dopamine or dobutamine.

Steps in the management of anaphylaxis:

1. **Sympathomimetic** Epinephrine (adrenaline) by intramuscular injection using epinephrine injection 1 in 1000, **ADULT** and **ADOLESCENT**, 500 micrograms (0.5 ml); **INFANT** under 6 months 50 micrograms (0.05 ml); **CHILD** 6 months–6 years 120 micrograms (0.12 ml), 6–12 years 250 micrograms (0.25 ml)

   *Note.* The above doses may be repeated several times if necessary at 5-minute intervals, according to blood pressure, pulse, and respiratory function

   If circulation inadequate, by slow intravenous injection using epinephrine injection 1 in 10 000 (given at a rate of 1 ml/minute), **ADULT** 500 micrograms (5 ml); **CHILD** 10 micrograms/kg (0.1 ml/kg), given over several minutes

2. **Vital functions** Maintain an open airway; give oxygen by mask, restore blood pressure (lay patient flat, raise feet)

3. **Antihistamine** such as chlorpheniramine by intravenous injection over 1 minute, **ADULT** 10–20 mg, repeated if required (maximum total dose 40 mg in 24 hours)
4. **Corticosteroids** such as hydrocortisone *by slow intravenous injection*, ADULT 100–300 mg; CHILD up to 1 year, 25 mg; 1–5 years, 50 mg; 6–12 years, 100 mg

5. **Intravenous fluids:** start infusion with sodium chloride (0.5–1 litre during the first hour)

6. If the patient has asthma-like symptoms, give salbutamol 2.5–5 mg by nebulization or aminophylline 5 mg/kg *by intravenous injection* over at least 20 minutes.

**Antihistamine**

**Sedating antihistamine**

**CHLORPHENIRAMINE MALEATE**

Chlorpheniramine is a representative sedative antihistamine.

*Tablets*, chlorphenamine maleate 4 mg

*Elixir* (Oral solution), chlorphenamine maleate 2 mg/5 ml

*Injection* (Solution for injection), chlorphenamine maleate 10 mg/ml, 1-ml ampoule

**Uses:**
symptomatic relief of allergy, allergic rhinitis (hay fever) and conjunctivitis, urticaria, insect stings and pruritus of allergic origin; adjunct in the emergency treatment of anaphylactic shock and severe angioedema

**Contraindications:**
prostatic enlargement, urinary retention; ileus or pyloroduodenal obstruction; glaucoma; child under 1 year

**Precautions:**
pregnancy and breastfeeding (Appendices 2 and 3); renal and hepatic impairment (Appendices 4 and 5); epilepsy; interactions: Appendix 1

**SKILLED TASKS.**
May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage:**
Allergy, *by mouth*, ADULT 4 mg every 4–6 hours (maximum 24 mg daily); CHILD under 1 year not recommended, 1–2 years 1 mg twice daily, 2–5 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, *by subcutaneous or intramuscular injection*

ADULT 10–20 mg, repeated if required (maximum 40 mg in 24 hours); by subcutaneous injection CHILD 87.5 micrograms/kg, repeated if necessary up to 4 times daily

Anaphylaxis (adjunct), by intravenous injection over 1 minute,

ADULT 10–20 mg; child under 1 year 250 micrograms/kg, 1–5 years 2.5–5 mg, 6–12 years 5–10 mg

Adverse effects:
drowsiness (rarely paradoxical stimulation with high doses, or in children or elderly), hypotension, headache, palpitations, psychomotor impairment, urinary retention, dry mouth, blurred vision, gastrointestinal disturbances; liver dysfunction; blood disorders; also rash and photosensitivity reactions, sweating and tremor, hypersensitivity reactions (including bronchospasm, angiodema, anaphylaxis); injections may be irritant

PROMETHAZINE

Promethazine is a representative of older antihistamine.

Injection, 25mg/ml, 2mg, × 2ml

Tablets, 25mg

Uses:
Symptomatic treatment of various allergic conditions: antiemetic; motion sickness; sedative; analgesic adjunct for control of postoperative pain; anesthetic adjunct; emergency treatment of anaphylactic reactions

Precautions
Pregnancy: crosses the placenta. Possible respiratory depression if drug is administered near time to delivery. Lactation: Enters breast milk/not recommended

Dosage:
CHILDREN: Antihistamine: oral, rectal: 0.1mg/kg/dose every 6 hours during the day and 0.5mg/kg/ dose at bedtime
Anti-emetic: Oral; I V; IM; RECTAL: 0.25-1mg/kg 4-6 times/day as needed
Motion Sickness: Oral; Rectal:0.5mg/kg/dose 30mins -1 hour before departure, then every 12hours as needed.
Sedation: Oral; IM; IV; Rectal: 0.5-1mg/kg/dose every 6 hours as needed

ADULTS:
Antihistamine: oral, rectal: 12.5mg 3 times a day and 25mg at bedtime
IM, IV: 25mg, may repeat in 2 hours when necessary: switch to oral route as soon as feasible
Anti-emetic: Oral; I V; I M; rectal: 12.5mg-25mg every 4 hours as needed

Motion Sickness: Oral, Rectal: 25mg 30mins – 60 mins before departure, then every 12hours as needed. Sedation: Oral; IM; IV; Rectal: 25-50mg dose

**Adverse effects:**
Drowsiness, postural hypotension, tachycardia, dizziness; nonspecific QT changes, dystonias, akathisia, pseudoparkinsonism, tardive dyskinesia, neuroleptic dyndrome, seizures and skin pigmentation.

**KETOTIFEN**

*Tablets: 1mg,*

*Syrup: 1mg/5mls*

**Uses**
Antihistamine due to allergic reactions, prophylaxis of asthma

**Precautions**
Previous antiasthmatic treatment should be continued for a minimum of two weeks after initiation of ketotifen treatment, avoid with oral antidiabetic (fall in thrombocytes have been reported); use with caution in lactation

**Dosage**
1 mg twice a day with food, increase if necessary to 2mg twice a day; initial treatment in readily sedated patients 0.5-1mg at night; child over two years 1mg twice a day

**Adverse effects**
Drowsiness, dizziness, dry-mouth, weight gain, CNS stimulation

**Patient Information:** take with food.

Non-Sedating Antihistamines

**LORATIDINE**

*Tablet, 10mg*

Loratidine is a representative of the second generation antihistamines.

**Use**
Symptomatic relief to allergic reaction such as hay fever, urticaria

**Precautions:**
Use with caution in hepatic and renal impairment

Lactation: Enters breast milk, not recommended

**Dosage:**
**ADULT** and **CHILD** over 6years 10mg daily; Child 2-5mg 5mg daily

**Adverse effects:**
3.1 Antiallergics and drugs used in anaphylaxis

Headaches, somnolence, fatigue, xerostoma, nervousness, rash, abdominal pain, hyperkinesias, wheezing, conjunctivitis, dysphonia

**Sympathomimetic**

**Epinephrine (adrenaline)**

*Injection* (Solution for injection), epinephrine (as hydrochloride or hydrogen tartrate) 1 mg/1 ml, 1-ml ampoule

**Uses:**
Severe anaphylactic reaction; severe angioedema; cardiac arrest (section 12.2)

**Precautions:**
hyperthyroidism, hypertension, diabetes mellitus, heart disease, arrhythmias, cerebrovascular disease; second stage of labour; elderly; **interactions:** Appendix 1

**Dosage:**
Caution: Different dilutions of epinephrine injection are used for different routes of administration

Anaphylaxis, by *intramuscular or subcutaneous injection* of 1:1000 epinephrine injections, (see steps in the Management of Anaphylaxis for doses

Anaphylaxis, by *slow intravenous injection* of 1:10 000 epinephrine injection. This route should be reserved for severely ill patients when there is doubt about the adequacy of circulation and absorption from the intramuscular site, see Steps in the Management of Anaphylaxis for doses

**Adverse effects:**
Tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, hyperglycaemia, dizziness, pulmonary oedema have all been reported; headache common

**DOPAMINE**

Injection: 40mg/ml, 5ml amp

**Use**
Adjunct in the treatment of shock (Cardiogenic shock, endotoxic shock, cardiac failure)

**Contraindications**
Tachyarrhythmias, ventricular fibrillation, pheochromocytoma

**Precautions**
Patients with occlusive vascular disease. Dopamine must not be used as sole therapy during hypovolemia, fluid must be replaced.

**Dosage**


I.V. infusion (Administration requires the use of an infusion pump):

**NEONATES**: 1-20 mcg/kg/minute continuous infusion, titrate to desired response  
**CHILDREN**: 1-20 Mcg/kg/minute, Maximum: 50mcg/kg/minute continuous infusion, titrate to desired response  
**ADULTS**: 1-20 mcg/kg/minute up to 20mcg/kg/minute, titrate to desired response. Infusion may be increased by 1-4 mcg/kg/minute at 10-30 minute intervals until optimal response is obtained  

Administration: Administered into large vein to prevent possibility of extravasation, monitor continuously for free flow; use infusion device to control rate of flow, gradually decrease the dose of dopamine (sudden discontinuation cause hypotension)

To prepare for infusion:

\[
6 \times \text{weight (kg)} \times \text{desired dose (mcg/kg/minute)} = \text{mg of drug to be added to 100ml}
\]

of i.v. fluid

I.V. infusion rate (ml/h)

**Adverse effects**
Nausea, peripheral vasoconstriction, tachycardia, angina pain, palpitations, dyspnea, serum glucose increase, necrosis and sloughing of surrounding tissues, increase intraocular pressure.

**DOBUTAMINE**

*Injection*: 12.5mg/ml, 20ml vial  

**Use**
Inotropic support in infarction, cardiac surgery, cardiomyopathies and cardiogenic shock  

**Contraindications**: idiopathic hypertrophic subaortic stenosis  

**Precaution**: correct hypovolemia and atrial fibrillation can cause sensitivity in asthmatics; can cause increase in heart rate, patients with atrial fibrillation may experience an increase in ventricular response, use with caution in post MI  

**Dosage**:
Administration requires an infusion pump:  

**NEONATES**: 2-15 mcg/kg/minute  

**CHILDREN and ADULTS**: 2.5-5mcg/kg/minute, maximum: 40 mcg/kg/minute  

Administration: Administered into large vein; use infusion device to control rate of flow, do not administer through the same I.V. line as: heparin, hydrocortisone sodium succinate,
3.1 Antiallergics and drugs used in anaphylaxis

Cefazolin or penicillin.
To prepare for infusion:

\[
6 \times \text{weight (kg)} \times \text{desired dose (mcg/kg/minute)} = \text{mg of drug to be added to 100ml of I.V. fluid}
\]

I.V. infusion rate (ml/h)

**Adverse effects:**
Tachycardia and significant increase in systolic blood pressure, hypotension, angina pain, premature ventricular beats, palpitations

**Antiinflammatory**

**DEXAMETHASONE**

*Tablets*, dexamethasone 500 micrograms, 4 mg

*Injection* (Solution for injection), dexamethasone phosphate (as sodium salt), 4 mg/ml, 1-ml ampoule

**Uses**
Adjunct in the emergency treatment of anaphylaxis; short-term suppression of inflammation in allergic disorders; for other indications see section 18.1

**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 patient (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; for further precautions relating to long-term use of corticosteroids see section 18.1

**Dosage**
Allergy (short-term use), *by mouth*, ADULT and CHILD, usual range 0.5–10 mg daily as a single dose in the morning

Anaphylaxis, *by slow intravenous injection or infusion*, ADULT 0.5–20 mg; CHILD 200–500 micrograms/kg

**Adverse effects**
Nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; perineal irritation after intravenous administration; for adverse effects associated with long-term corticosteroid treatment see section 18.1

HYDROCORTISONE

*Injection* (Powder for solution for injection), hydrocortisone (as sodium succinate), 100-mg vial

**Uses**
Adjunct in the emergency treatment of anaphylaxis; inflammatory skin conditions (section 13.3); inflammatory bowel disease (section 17.4); adrenocortical insufficiency (section 18.1)

**Contraindications**
Not relevant to emergency use but for contra-indications relating to long-term use see section 18.1

**Precautions:**
Not relevant to emergency use but for precautions relating to long-term use see section 18.1

**Dosage:**
Anaphylaxis, *by slow intravenous injection* as a single dose, see Steps in the Management of Anaphylaxis (above)

**Adverse effects:**
For adverse effects associated with long-term corticosteroid treatment see section 18.1

PREDNISOLONE

*Tablets*, prednisolone 5 mg, 25 mg

**Uses:**
Short-term suppression of inflammation in allergic disorders; longer-term suppression (section 18.1); malignant disease (section 8.3); eye (section 21.2)

**Contraindication**
Untreated systemic infection; 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 patient (varicella–zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; for further precautions relating to long-term use of corticosteroids see section 18.1

**Dosage**
Allergy (short-term use), *by mouth*, ADULT and CHILD, initially up to 10–20 mg daily as a single dose in the morning (in severe allergy up to 60 mg daily as a short course of 5–10 days)

**Adverse effects:**
Nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; for adverse effects associated with long-term corticosteroid treatment see section 18.1
METHYLPREDNISONE

Injection, 500mg; 2ml

Use
Primarily as an anti-inflammatory or immunosuppressant agent in the treatment of a variety of diseases including those of hematologic, allergic, inflammatory, neoplastic, and autoimmune origin. Prevention and treatment of graft-versus-host disease following allogeneic bone marrow transplantation. Treatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin

Contraindications
Hypersensitivity to methylprednisolone or any component of the formulation; viral, fungal, or tubercular skin lesions; administration of live virus vaccines; serious infections, except septic shock or tuberculous meningitis. Methylprednisolone formulations containing benzyl alcohol preservative are contraindicated in infants.

Precautions
Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal, prolonged use of corticosteroids may also increase the incidence of secondary infection, acute myopathy has been reported with high dose corticosteroids, prolonged treatment with corticosteroids has been associated with the development of Kaposi’s sarcoma (case reports); if noted, discontinuation of therapy should be considered, long-term use has been associated with fluid retention and hypertension. Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia, use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk, use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention., use with caution in patients with renal impairment; fluid retention may occur.

Adverse Reactions
Edema, hypertension, arrhythmia, insomnia, nervousness, vertigo, seizure, psychoses, pseudotumor cerebri, headache, mood swings, delirium, hallucinations, euphoria, hirsutism, acne, skin atrophy, bruising, hyperpigmentation, diabetes mellitus, adrenal suppression, hyperlipidemia, cushing’s syndrome, pituitary-adrenal axis suppression, growth suppression, glucose intolerance, hypokalemia, alkalosis, amenorrhea, sodium and water retention, hyperglycemia, increased appetite, indigestion, peptic ulcer, nausea, vomiting, abdominal distention, ulcerative esophagitis, pancreatitis, transient leukocytosis, arthralgia, muscle weakness, osteoporosis, fractures

Dosage:

By intramuscular injection or slow intravenous injection or infusion, initially 10-500mg; graft rejection up to 1g daily by intravenous infusion for up to 3 days.
Section 4: Antidotes and other substances used in poisonings

4.1 General care and non-specific treatment
4.2 Specific antidote
4.2.1 Paracetamol overdose
4.2.2 Opioid analgesic overdose
4.2.3 Organophosphate and carbamate poisoning
4.2.4 Iron poisoning and iron and aluminium overload
4.2.5 Heavy metal poisoning
4.2.6 Methaemoglobinemia
4.1 General care and non-specific treatment

All patients who show features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed actions should also be admitted, even if they appear well; delayed-action poisons include acetylsalicylic acid, iron, lithium, paracetamol, paraquat, tricyclic antidepressants and warfarin. The effects of modified-release or prolonged-release preparations are also delayed. However, it is often impossible to establish with certainty the identity of the poison and the size of the dose but information on the type and timing of poisoning may be useful for symptomatic management. Few patients require active removal of the poison.

Most patients must be treated symptomatically and monitored. Particular care must be given to maintenance of respiration and blood pressure. Assisted ventilation may be required. Cardiac conduction defects and arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities. Hypothermia which may develop in patients who have been unconscious for some hours is best treated by wrapping the patient in blankets to conserve body heat. Convulsions which are prolonged or recurrent may be controlled by intravenous diazepam. In some situations removal of the poison from the stomach by gastric lavage may be appropriate (see below). Activated charcoal can bind many poisons in the stomach and therefore prevent absorption. Active elimination techniques such as repeated administration of activated charcoal can enhance the elimination of some drugs after they have been absorbed (see below). Other techniques to enhance elimination of poisons after their absorption are only practical in hospital and are only suitable for a small number of patients and only to a limited number of poisons. Methods include haemodialysis and haemoperfusion. Alkalization of urine can be used to increase the elimination of salicylates. Forced alkaline diuresis is no longer recommended.

Gastric lavage

The dangers of attempting to empty the stomach have to be balanced against the toxicity of the ingested poison, as assessed by the quantity ingested, the inherent toxicity of the poison, and the time since ingestion. Gastric emptying...
is clearly unnecessary if the risk of toxicity is small or if the patient presents too late. Emptying the stomach may be of value if undertaken within 1–2 hours after ingestion. The main risk is with inhalation of stomach contents and gastric lavage should not be undertaken in drowsy or comatose patients without assistance of an anaesthetist so that the airway can be protected by a cuffed endotracheal tube. Gastric lavage must not be attempted after corrosive poisoning or for hydrocarbon products which could be dangerous if aspirated.

**Emesis**

Induction of emesis for the treatment of poisoning is not recommended. There is no evidence that it prevents absorption of the poison and it may increase the likelihood of aspiration. Furthermore, the effects of the emetic substance may complicate diagnosis.

**Prevention of absorption**

Given by mouth activated charcoal can bind many poisons in the gastrointestinal system, thereby reducing their absorption. The sooner it is given, the more effective it is, but it may be effective for up to 1 hour after ingestion of the poison. It may be effective several hours after poisoning with modified-release preparations or drugs with anticholinergic (antimuscarinic) properties. It is relatively safe and particularly useful for prevention of absorption of poisons which are toxic in small amounts, for example, antidepressants. Furthermore, repeated doses of activated charcoal enhance the faecal elimination of some drugs (that undergo enterohepatic or enteroenteric recycling) several hours after ingestion and after they have been absorbed, for example phenobarbital, theophylline.

**Activated charcoal**

*Powder* (Powder for oral suspension), activated charcoal

**Uses:**

Treatment of acute poisoning

**Contraindications:**

Poisoning by hydrocarbons with high potential for harm if aspirated; poisoning by corrosive substances—may prevent visualization of lesions caused by poison

**Precautions:**

Drowsy or unconscious patients—risk of aspiration (intubate before administration via nasogastric or gastric tube); not effective for poisoning with alcohols, clofenotane (dicophane,
4.2 Specific antidotes

DDT), cyanides, Malathion, and metal salts including iron and lithium

**Dosage:**
Poisoning (prevention of absorption), by mouth, **ADULT** 50–100 g as a single dose, as soon as possible after ingestion of poison; **INFANT** 1 g/kg as a single dose; **CHILD** 1–12 years, 25 g as a single dose (50 g in severe poisoning)
Poisoning (active elimination), by mouth, **ADULT** and **CHILD** over 1 year, 25–50 g initially, then 25–50 g every 4–6 hours; **INFANTS** 1 g/kg every 4–6 hours

**Adverse effects:**
Black stools; vomiting, constipation or diarrhoea; pneumonitis—due to aspiration

**4.2 Specific antidotes**

**Paracetamol overdosage**

As little as 10–15 g or 150 mg/kg of paracetamol taken within 24 hours may cause severe hepatocellular necrosis and less frequently renal tubular necrosis. The only early features of poisoning, nausea and vomiting, usually settle within 24 hours. Persistence beyond this time, often with the onset of right sub-costal pain and tenderness, usually indicates the development of liver damage which is maximal 3–4 days after ingestion. In spite of a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently.

Administration of activated charcoal should be considered if paracetamol in excess of 150 mg/kg or 12 g, whichever is smaller, is thought to have been ingested within the previous hour.

**Acetylcysteine** protect the liver if given within 10–12 hours of ingesting paracetamol. Acetylcysteine, given intravenously is most effective within 8 hours of overdosage, but is effective for up to and possibly beyond 24 hours. Alternatively, methionine may be given by mouth provided the overdose was ingested within 10–12 hours and the patient is not vomiting. However, acetylcysteine is the preferred treatment. Concurrent use of activated charcoal and specific oral antidotes should be avoided.

Once the patient is in hospital the need to continue antidote treatment can be assessed from plasma-paracetamol concentrations.
ACETYLCYSTEINE

Injection (Concentrate for dilution for infusion), acetylcysteine 200 mg/ml, 10-ml ampoule

Uses:
Paracetamol overdosage

Precautions:
Asthma

Dosage:
Paracetamol overdosage, by intravenous infusion, ADULT and CHILD initially, 150 mg/kg in 200 ml glucose 5% over 15 minutes, followed by 50 mg/kg in 500 ml glucose 5% over 4 hours, then 100 mg/kg in 1000 ml glucose 5% over 16 hours. Note. Children are given the same doses of acetylcysteine as adults, but the volume of infusion may need to be reduced to avoid fluid overload

Adverse effects:
Hypersensitivity reactions including rashes, anaphylaxis

4.2.2 Opioid analgesic overdosage

Opioids cause varying degrees of coma, respiratory depression and pinpoint pupils. Naloxone is a specific antidote indicated if there is coma or bradypnoea. Naloxone has a shorter duration of action than many opioids so close monitoring and repeated injections are required depending on respiratory rate and depth of coma; naloxone may alternatively be given by intravenous infusion. The effects of some opioids such as buprenorphine are only partially reversed by naloxone.

Acute withdrawal syndromes may be precipitated by the use of naloxone in patients with a physical dependence on opioids or in overdosage with large doses; a withdrawal syndrome may occur in neonates of opioid-dependent mothers.

NALOXONE HYDROCHLORIDE

Injection (Solution for injection), naloxone hydrochloride 400 micrograms/ml, 1-ml ampoule

Uses
Opioid overdosage; postoperative respiratory depression

Precautions
Physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated (see above); pregnancy (Appendix 2); breastfeeding (Appendix 3); cardiovascular disease

Dosage
Overdosage of opioids, by intravenous injection, ADULT
0.8–2 mg repeated at intervals of 2–3 minutes to a maximum of 10 mg, if respiratory function does not improve, question diagnosis; CHILD 10 micrograms/kg; a subsequent dose of 100 micrograms/kg if no response

**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)

Overdosage of opioids, by continuous intravenous infusion using an infusion pump, **ADULTS** 10 mg diluted in 50 ml glucose 5% intravenous infusion at a rate adjusted according to response

**Adverse effects:**

Nausea, vomiting, sweating—may also be due to opioid withdrawal

Flumazenil is a benzodiazepine antagonist for reversal of the central sedative effects of benzodiazepines after anaesthesia and similar procedures.

**FLUMAZENIL**

*Injection,* 100 micrograms/ml

**Use**

Reversal of sedative effects of benzodiazepines in anaesthetic, intensive care, and diagnostic

**Precautions**

Short acting (repeat doses may be necessary-benzodiazepine effects may persist for at least 24 hours); benzodiazepine dependence (may precipitate withdrawal symptoms); ensure neuromuscular blockade cleared before giving; avoid rapid injection in high risk anxious patients and following major surgery; hepatic impairment; head injury (rapid reversal of benzodiazepine sedation may cause convulsions); elderly, children, pregnancy and breast feeding

**Contraindications**

Life treating condition (e.g. raised intracranial pressure, status epilepticus) controlled by benzodiazepines

**Adverse effects**

Nausea, vomiting, and flushing, if wakening too rapid, agitation, anxiety, and fear, transient increase in blood pressure and heart rate in intensive care patients

**Dosage**

*By intravenous injection,* 200 micrograms over 15 seconds, then 100 micrograms at 60-second intervals if required; usual dose range, 300mcg-600mcg; max. total dose 1mg (2 mg in intensive care)

4.2.3 Organophosphate and carbamate poisoning

Organophosphates are absorbed through the bronchi and intact skin as well as from the gastrointestinal tract. Initial treatment of organophosphate or carbamate poisoning includes prevention of further absorption by emptying the stomach by gastric lavage, moving patient to fresh air supply, removing contaminated clothing and washing contaminated skin. A clear airway must be maintained.

Organophosphates inhibit cholinesterases and thus prolong the effects of acetylcholine. Toxicity depends on the particular compound involved, and onset after skin exposure may be delayed. Atropine will reverse the muscarinic effects of acetylcholine and is used (in conjunction with oximes such as pralidoxime) with additional symptomatic treatment.

Additional treatment for carbamate poisoning is generally symptomatic and supportive. Atropine may be given but may not be required because of the rapidly reversible type of cholinesterase inhibition produced (oximes should not be given).

ATROPINE SULFATE

Injection (Solution for injection), atropine sulfate 1 mg/ml, 1-ml ampoule

Uses:
Organophosphate and carbamate poisoning; premedication; antispasmodic; mydriasis and cycloplegia

Precautions:
Children, elderly, Down syndrome; angle-closure glaucoma; myasthenia gravis; gastrointestinal disorders; prostatic enlargement; cardiac disorders; pyrexia; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Organophosphate poisoning, by intramuscular or intravenous injection (depending on severity of poisoning), ADULT 2 mg (child 20 micrograms/kg) every 5–10 minutes until the skin becomes flushed and dry and tachycardia develops

4.2.4 Iron poisoning and iron and aluminium overload

Mortality from iron poisoning is reduced by specific therapy with deferoxamine which chelates iron. Before administration of deferoxamine the stomach should be emptied by gastric lavage (with a wide-bore tube) within 1 hour of ingesting a significant amount of iron.
quantity of iron or if radiography reveals tablets in the stomach. Deferoxamine is also used to diagnose and treat chronic iron overload. It is used in the diagnosis of aluminium overload and to treat aluminium overload in patients with end-stage renal failure undergoing maintenance haemodialysis.

**DEFEROXAMINE MESILATE**

*Injection* (Powder for solution for injection or infusion), deferoxamine mesilate 500-mg vial

**Uses:**
Acute iron poisoning; chronic iron overload; aluminium overload

**Precautions:**
Renal impairment (Appendix 4); eye and ear examinations before and at 3-month intervals during treatment; aluminium encephalopathy (may exacerbate neurological dysfunction); pregnancy (Appendix 2); breastfeeding (Appendix 3); children under 3 years (may retard growth)

**Dosage:**
Acute iron poisoning, by *slow intravenous infusion*, ADULT and CHILD initially 15 mg/kg/hour, reduced after 4–6 hours so that total dose does not exceed 80 mg/kg in 24 hours
Chronic iron overload, by *subcutaneous or intravenous infusion*, ADULT and CHILD lowest effective dose, usually within range of 20–60 mg/kg/day on 4–7 days a week
Aluminium overloads in end-stage renal failure, by *intravenous infusion*, ADULT and CHILD 5 mg/kg, once a week during last hour of dialysis
Diagnosis of iron overload, by *intramuscular injection*, ADULT and CHILD 500 mg
Diagnosis of aluminium overload, by *intravenous infusion*, ADULT and CHILD 5 mg/kg during last hour of dialysis

**RECONSTITUTION AND ADMINISTRATION.** According to manufacturer’s directions. For full details and warnings relating to administration for therapeutic or diagnostic purposes, see manufacturer’s literature

**Adverse effects:**
anaphylaxis; flushing, urticaria, hypotension, shock (especially if given by too rapid intravenous infusion); gastrointestinal disturbances; fever, headache, arthralgia, myalgia; arrhythmias; renal impairment; blood disorders; neurological disturbances including neuropathy, paraesthesia, and dizziness; convulsions; Yersinia and mucormycosis infections; visual disturbances (including lens opacity and retinopathy) and hearing loss; rash; rarely, growth retardation (in young children); rarely, adult respiratory distress syndrome; pain on intramuscular or subcutaneous injection; local irritation on prolonged subcutaneous
infusion; reddish-brown discoloration of urine
Calcium gluconate subcutaneous injection is used for dermal exposures of toxic levels of Hydrofluoric acid and Magnesium.

CALCIUM GLUCONATE

Calcium gluconate is a complementary drug
Injection (Solution for injection), calcium gluconate (monohydrate) 100 mg (Ca²⁺ 220 micromol)/ml, 10-ml ampoule
Uses:
See as above
Contraindications:
conditions associated with hypercalcaemia and hypercalciuria
Precautions:
Monitor plasma calcium concentration; interactions: Appendix 1
Dosage:
Infiltrate each square centimeter of exposed area with 0.5ml of 10% solution of calcium gluconate S.C using a 30-gauge needle. 1ml/kg I.V of a 105 solution for magnesium toxicity (intra-arterial injection)
Adverse effects:
Mild gastrointestinal disturbances; bradycardia, arrhythmia; irritation at injection site

4.2.5 Heavy metal poisoning

Heavy metal poisoning may be treated with a range of antidotes including, penicillamine. Penicillamine is also used to promote excretion of copper in Wilson disease.

PENICILLAMINE

Capsules, penicillamine 125 mg, 250 mg
Tablets, penicillamine 125 mg, 250 mg

Uses:
Poisoning by heavy metals, particularly lead and copper; Wilson disease; severe rheumatoid arthritis (section 2.4)
Contraindications:
Hypersensitivity; lupus erythematosus
Precautions:
Monitor throughout treatment including blood counts and urine tests; renal impairment (Appendix 4); pregnancy (Appendix 2); avoid concurrent gold, chloroquine or immunosuppressive treatment; avoid oral iron within 2 hours of a dose; interactions: Appendix 1
**Blood counts.**
In Wilson disease, consider withdrawal if platelet count falls below 120 000/mm³ or white blood cells below 2500/mm³ or if 3 successive falls within reference range (can restart at reduced dose when counts return to reference range but permanent withdrawal necessary if neutropenia or thrombocytopenia recur)

**Patient Advice.**
In Wilson disease warn patient to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers or rash develop

**Dosage:**
Heavy metal poisoning, by mouth, ADULT 1–2 g daily in 4 divided doses before food (continue until urinary lead stabilised at less than 500 micrograms/day); CHILD 20–25 mg/kg daily in divided doses

Wilson disease, by mouth, ADULT 1.5–2 g daily in divided doses before food; maximum 2 g daily for 1 year then maintenance 0.75–1 g daily; ELDERLY 20 mg/kg daily in divided doses adjusted according to response; CHILD up to 20 mg/kg daily in divided doses; minimum 500 mg daily

**Adverse effects:**
Initially nausea (less of a problem if taken with food and on retiring), anorexia, fever; taste loss (mineral supplements not recommended); blood disorders including thrombocytopenia, neutropenia, agranulocytosis and aplastic anaemia; proteinuria, rarely haematuria (withdraw immediately); haemolytic anaemia, nephrotic syndrome, lupus erythematosus-like syndrome, myasthenia gravis-like syndrome, polymyositis (rarely with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alopecia, bronchiolitis and pneumonitis, pemphigus, Goodpasture syndrome and Stevens-Johnson syndrome also reported; male and female breast enlargement reported; rash early in treatment (usually allergic—may need temporary withdrawal), late rashes (reduce dose or withdraw treatment)

4.2.5 Heavy metal poisoning

**Methaemoglobinemia**
Methylthioninium chloride can lower the levels of methaemoglobin in red blood cells and is used in the treatment of methaemoglobinemia. In large doses, it may cause methaemoglobinemia and therefore methaemoglobin levels should be monitored during treatment.

**METHYLTHIONINIUM CHLORIDE**
Methylen Blue
Injection (Solution for injection), methylthioninium chloride 10 mg/ml, 10-ml ampoule
Uses:
Acute methaemoglobinaemia

Contraindications:
Severe renal impairment; methaemoglobinaemia due to chlorate or induced by sodium nitrite in treatment of cyanide poisoning

Precautions:
G6PD deficiency—may cause haemolytic anaemia; monitor blood methaemoglobin throughout treatment; pregnancy; breastfeeding

Dosage:
Acute methaemoglobinaemia, by slow intravenous injection over several minutes ADULT and CHILD 1–2 mg/kg as a single dose; may be repeated after 1 hour if required

ADMINISTRATION.
According to manufacturer’s directions

Adverse effects:
Nausea, vomiting, abdominal pain, chest pain, headache, dizziness, confusion, profuse sweating; hypertension or hypotension reported; haemolytic anaemia—in G6PD deficiency; methaemoglobinaemia—with high dosage; bluish skin discolouration; blue saliva, urine and faeces
SECTION 5.

ANTICONVULSANTS/ ANTIEPILEPTICS

5.1 Control of epilepsy
5.1 Control of epilepsy

Treatment should always be started with a single drug, but the choice of an anticonvulsant can only be made on an individual basis and will depend on the efficacy of the drug and the patient's tolerance of treatment. If a drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not tolerated, it should be gradually substituted with another with the first drug being withdrawn only when the new regimen is mainly established. If monotherapy is ineffective, two drugs should be given in combination and several regimens may need to be tried before the most appropriate is found.

Initial dose of the drug of choice should be determined on the basis of the degree of urgency, the size and age of the patient. It should be increased gradually until an effective response is obtained. All antiepileptics commonly produce neurological adverse effects at too high a dose, and patients should be monitored closely for adverse effects to help in accurate dose titration. Except for phenytoin, it is rarely useful to measure plasma-drug concentrations as an aid to dose adjustment. Non-compliance because of inappropriate dosing and overdosing is a major impediment to effective antiepileptic treatment. Patients should ideally remain under supervision throughout treatment.

WITHDRAWAL

Treatment is normally continued for a minimum of two years after the last seizure. Withdrawal should be extended over a period of several months because abrupt withdrawal can lead to complications such as status epilepticus. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time. Many adult patients relapse once treatment is withdrawn and it may be justified to continue treatment indefinitely, particularly when the patient's livelihood or lifestyle can be endangered by recurrence of a seizure.

PREGNANCY AND BREASTFEEDING

Untreated epilepsy during pregnancy may cause harm to the fetus; there is therefore no justification for abrupt withdrawal of treatment although withdrawal of therapy may be an option if the patient has been seizure-free for at least 2 years; resumption of treatment may be considered after the first trimester. If antiepileptics are continued in pregnancy, monotherapy with the lowest effective dose is preferred, with adjustment made to take account of changes in plasma levels associated with pregnancy. There is an increased risk of birth defects with the Belize Drug Formulary and Therapeutics Manual Ninth Edition 2009-2011.
use of anticonvulsants, particularly carbamazepine, valproate and phenytoin. However, if there is good seizure control, there is probably no advantage in changing pregnant patients' antiepileptic drugs. In view of the risks of neural tube and other defects, patients who may become pregnant should be informed of the risks and referred for advice, and pregnant patients should be offered counselling and antenatal screening. To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding associated with carbamazepine, phenobarbital and phenytoin, prophylactic phytomenadione (vitamin K₁) is recommended for the neonate and the mother before delivery. Antiepileptic drugs can be continued during breastfeeding (see also Appendix 3).

**DRIVING**

Regulations are in place in many countries which may, for example, restrict driving by patients with epilepsy to those whose seizures are controlled. Further, antiepileptic drugs may cause CNS depression, particularly in the early stages of treatment and patients affected by adverse effects such as drowsiness or dizziness should not operate machinery or drive.

**Choice of antiepileptic in management of convulsive disorders**

**GENERALIZED TONIC-CLONIC, SIMPLE PARTIAL AND COMPLEX PARTIAL SEIZURES**

Carbamazepine, phenobarbital, phenytoin, and valproate are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of haematological and hepatic function is often advised, particularly for carbamazepine and valproate.

**ABSENCE SEIZURES**

Both ethosuximide and valproate are widely used in the treatment of absence seizures (petit mal) and are usually well tolerated. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses which call for immediate, but cautious, discontinuation. Absence seizures are commonly associated with tonic-clonic seizures and valproate is preferred since it is effective in both disorders.

**TONIC SEIZURES, ATONIC SEIZURES AND ATYPICAL ABSENCE SEIZURES**

Phenobarbital or phenytoin is widely used for tonic seizures, valproate or clonazepam for atonic seizures, and clonazepam for atypical absence seizures.

MYOCLONIC SEIZURES

Valproate is widely used and most effective for juvenile myoclonic seizures. However, both valproate and this type of seizure are associated with a high relapse rate and it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. Valproate or clonazepam can be of value in this case and other antiepileptic drugs may be useful in intractable cases. Both drugs are generally well accepted, although tolerance to clonazepam has been reported.

INFANTILE SPASM (INFANTILE MYOCLOMNIC EPILEPSY)

Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. Clonazepam is sometimes of value in resistant cases.

FEBRILE CONVULSIONS

Brief febrile convulsions usually respond to sponging with tepid water and by giving an antipyretic such as paracetamol (section 2.1.2). Recurrent febrile convulsions or prolonged convulsions (those lasting 15 minutes or longer) are treated with diazepam, either rectally in solution or by intravenous injection, to prevent possible brain damage. *Intermittent prophylaxis*, with diazepam administered at the onset of fever, may prevent recurrence of febrile convulsions, but only in a small proportion of children. Use of antiepileptics for *continuous prophylaxis* is controversial; it is probably indicated in only a small proportion of children including those whose first seizure occurred during the first 14 months of life, or who already have evident neurological abnormalities, or who have had previous prolonged or focal convulsions. Phenobarbital may be used for this purpose but careful clinical monitoring and dosage adjustment are necessary in order to minimize the risk of adverse effects. Valproate, although effective, is not recommended because of the greater risk of hepatotoxicity in young children.

Status Epilepticus.

Status epilepticus is a medical emergency which carries a high mortality rate. Initial management includes positioning the
patient to avoid injury, supporting respiration including provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia; maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, because the drugs used in its management may also depress respiration.

Intravenous diazepam or clonazepam are often effective in status epilepticus. Diazepam, which acts rapidly, should be administered first and should be followed immediately by a loading dose of phenytoin which has a longer-acting effect. When cannulation is impossible, diazepam may be administered rectally as a solution (absorption from suppositories is too slow for treatment of status epilepticus). Intravenous phenobarbital is also effective but is more likely to cause respiratory depression; it is used in refractory cases but should be avoided in patients who have recently received oral phenobarbital. Rectal paraldehyde may also be used; it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

If seizures continue despite treatment, general anaesthesia may be required. The underlying cause must be identified and remedied in all cases.

**CARBAMAZEPINE**

*Tablets*, carbamazepine 100 mg, 200 mg

**Uses:**
Generalized tonic-clonic and partial seizures; trigeminal neuralgia; bipolar disorder (section 24.2.2)

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

**Precautions:**
Hepatic impairment (Appendix 5); renal impairment (Appendix 4); cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; pregnancy (important see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; interactions: Appendix 1

**BLOOD, HEPATIC OR SKIN DISORDERS.**

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

**Patient Advice.**
May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

**Dosage:**
Generalized tonic-clonic seizures, partial seizures, by mouth, **ADULT** initially 100 mg twice daily, increased gradually according to response to usual maintenance dose of 0.8–1.2 g daily in divided doses; **ELDERLY** reduce initial dose; **CHILD** 10–20 mg/kg daily in divided doses
Trigeminal neuralgia, by mouth, **ADULT** initially 100 mg 1–2 times daily increased gradually according to response; usual dose 200 mg 3–4 times daily with up to 1.6 g daily in some patients

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

**Adverse effects:**
dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma levels); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly

**CLONAZEPAM**
Drug subject to international control under the Convention on Psychotropic Substances (1971)
**Tablets**, clonazepam 1 milligrams

**Uses:**
Atonic seizures; myoclonic seizures; atypical absence seizures; absence seizures resistant to ethosuximide or valproate; infantile spasms

**Contraindications:**
Respiratory depression; acute pulmonary insufficiency; my-
asthenia gravis

Precautions:
Respiratory disease; hepatic impairment (Appendix 5); renal impairment (Appendix 4); elderly and debilitated; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; porphyria; interactions: Appendix 1

PatientAdvice.
May impair ability to perform skilled tasks, for example operating machinery, driving; effects of alcohol enhanced; see also notes above

Dosage:
Epilepsy (see Uses above), by mouth, ADULT initially 1 mg at night for 4 nights, increased gradually over 2–4 weeks to a usual maintenance dose of 4–8 mg daily in divided doses; ELDERLY (or debilitated patients) initial dose 500 micrograms increased as above; CHILD up to 1 year initially 250 micrograms increased as above to 0.5–1 mg daily in divided doses; 1–5 years initially 250 micrograms increased to 1–3 mg daily in divided doses; 5–12 years initially 500 micrograms increased to 3–6 mg daily in divided doses

Adverse effects:
Drowsiness, lethargy, ataxia, paradoxical aggression, irritability and mental changes; rarely blood disorders, abnormal hepatic function tests, excessive salivation

DIAZEPAM

Drug subject to international control under the Convention on Psychotropic Substances (1971)
Diazepam is a representative benzodiazepine anticonvulsant. Various drugs can serve as alternatives

Injection (Solution for injection), diazepam 5 mg/ml, 2-ml ampoule

Use
Status epilepticus; emergency management of recurrent seizures; febrile convulsions; seizures associated with poisoning and drug withdrawal; adjunct in acute alcohol withdrawal; premedication (section 1.3); anxiety disorders (section 24.3)

Contraindications
Respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis; avoid injections containing benzyl alcohol in neonates

Precautions
Respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 5), renal impairment (Appendix
4); avoid prolonged use and abrupt withdrawal; when given intravenously facilities for reversing respiratory depression with mechanical ventilation must be at hand (see below); porphyria; interactions: Appendix 1

**PRECAUTIONS FOR INTRAVENOUS INFUSION.**

Intravenous infusion of diazepam is potentially hazardous (especially if prolonged) calling for close and constant observation and best carried out in a specialist centre with intensive care facilities. Prolonged intravenous infusion may lead to accumulation and delay recovery

**Patient Advice.**

May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

**Dosage**

Status epilepticus or emergency management of recurrent epileptic seizures, **by slow intravenous injection** (at rate of 5 mg/minute), **ADULT** 10–20 mg, repeated if necessary after 30–60 minutes; may be followed by **intravenous infusion** to maximum 3 mg/kg over 24 hours; **by slow intravenous injection**, **CHILD** 200 to 300 micrograms/kg (or 1 mg per year of age); **by rectum** as solution, **ADULT** and **CHILD** over 10 kg, 500 micrograms/kg, **ELDERLY** 250 micrograms/kg; repeated if necessary every 12 hours; if convulsions not controlled, other measures should be instituted

Febrile convulsions (preferred treatment), **by rectum** as solution [injection solution may be used], **CHILD** over 10 kg, 500 micrograms/kg (maximum 10 mg), with dose repeated if necessary

Febrile convulsions (alternative treatment), **by slow intravenous injection**, **CHILD** 200–300 micrograms/kg (or 1 mg per year of age)

Drug or alcohol withdrawal, **by slow intravenous injection** (at rate of 5 mg/minute), **ADULT** 10 mg; higher doses may be required depending on severity of symptoms

Seizures associated with poisoning, **by slow intravenous injection** (at rate of 5 mg/minute), **ADULT** 10–20 mg

**Adverse effects:**

drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; 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; blood disorders and jaundice; hypotension and apnoea, pain and thrombophlebitis (with injection)

**ETHOSUXIMIDE**

Capsules, ethosuximide 250 mg

Syrup, ethosuximide 250 mg/5 ml

Uses:
absence seizures

Precautions:
hepatic or renal impairment; blood counts and hepatic and renal function tests recommended; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; porphyria; interactions: Appendix 1

BLOOD DISORDERS.
Patients or 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, mouth ulcers, bruising or bleeding develop

Patient Advice.
May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

Dosage:
Absence seizures, by mouth, ADULT and CHILD over 6 years initially 500 mg daily, increased by 250 mg at intervals of 4–7 days to a usual dose of 1–1.5 g daily (occasionally, up to maximum of 2 g daily); CHILD under 6 years initially 250 mg daily, increased gradually to usual dose of 20 mg/kg daily

Patient Advice.
Daily doses of 1 g and above should be taken as 2 or more divided doses

NOTE.
Plasma concentration for optimum response 40–100 mg/litre (300–700 micromol/litre)

Adverse effects:
gastrointestinal disturbances including anorexia, hiccups, nausea and vomiting, epigastric pain (particularly during initial treatment); weight loss, drowsiness, dizziness, ataxia, headache, depression, mild euphoria; rarely, rash including Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, disturbances of liver and renal function (see Precautions), haematological disorders including leukopenia, agranulocytosis, aplastic anaemia, thrombocytopenia, pancytopenia; gum hyperplasia, swelling of tongue, irritation, hyperactivity, sleep disturbances, night terrors, aggressiveness, psychosis, increased libido, myopia, vaginal bleeding, also reported

PHENOBARBITAL

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

Tablets, phenobarbital 30 mg, 60 mg
Elixir, 50mg/5ml

Injection (Concentrate for solution for injection), phenobarbital
sodium 200 mg/ml [not included on WHO Model List]

**Uses:**
Generalized tonic-clonic seizures; partial seizures; neonatal seizures; febrile convulsions; status epilepticus (see notes above)

**Contraindications:**
Porphyria; absence seizures

**Precautions:**
Elderly, debilitated, children (may cause behavioural changes); impaired renal function (Appendix 4) or hepatic function (Appendix 5), respiratory depression (avoid if severe); pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal;

**Interactions:**
Appendix 1

**Patient Advice.**
May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

**Dosage:**
Generalized tonic-clonic seizures, partial seizures, *by mouth*, 
**ADULT** 60–180 mg at night; **CHILD** up to 8 mg/kg daily

Febrile convulsions, *by mouth*, **CHILD** up to 8 mg/kg daily

Neonatal seizures, *by intravenous injection* (dilute injection 1 in 10 with water for injections), **neonate** 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/litre

Status epilepticus, *by intravenous injection* (dilute injection 1 in 10 with water for injections), **ADULT** 10 mg/kg at a rate of not more than 100 mg/minute (up to maximum total dose of 1 g); **CHILD** 5–10 mg/kg at a rate of not more than 30 mg/minute

**NOTE.**
For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect. Plasma concentration for optimum response 15–40 mg/litre (65–170 micromol/litre)

**Adverse effects:**
Sedation, mental depression, ataxia, nystagmus; allergic skin reactions including rarely, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme); paradoxical excitement, restlessness and confusion in the elderly; irritability and hyperactivity in children; megaloblastic anaemia (may be treated with folic acid); osteomalacia; status epilepticus (on treatment withdrawal); hypotension, shock, laryngospasm and apnoea (with intravenous injection)

**PHENYTOIN SODIUM**

*Tablets/capsule*, phenytoin sodium 100 mg
*Injection* (Solution for injection), phenytoin sodium 50 mg/ml, 5-ml ampoule,

**Syrup, 125mg/5ml**

**Uses:**
Generalized tonic-clonic seizures; partial seizures; status epilepticus

**Contraindications:**
Porphyria; avoid parenteral use in sinus bradycardia, sino-atrial block, second- and third-degree heart block, Stokes-Adams syndrome

**Precautions:**
hepatic impairment (reduce dose; Appendix 5); pregnancy (important, see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); diabetes mellitus; monitor blood counts; hypotension and heart failure (caution with parenteral use); intravenous administration—resuscitation facilities must be available; injection solution alkaline (irritant to tissues);

**interactions:** Appendix 1

**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)

**Patient Advice.**
May impair ability to perform skilled tasks, for example operating machinery, driving; see notes above

**Dosage:**
Generalized tonic-clonic seizures, partial seizures, *by mouth*,

**ADULT** initially 3–4 mg/kg daily (as a single dose or in 2 divided doses), increased gradually at intervals of 2 weeks as necessary (with plasma-phenytoin concentration monitoring); usual dose 200–500 mg daily; **CHILD** initially 5 mg/kg daily in 2 divided doses; usual dose range 4–8 mg/kg daily (maximum 300 mg)

**NOTE.**
Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre)

**Patient Advice.**
Preferably taken with or after food

Status epilepticus, *by slow intravenous injection or by intravenous infusion* (with blood pressure and ECG monitoring),

**ADULT** 15 mg/kg at a rate of not more than 50 mg/minute, as a loading dose; maintenance doses of about 100 mg *by mouth* or *by slow intravenous injection* should be given thereafter at intervals of 6–8 hours, monitored by measurement of plasma concentrations; rates and dose reduced according to weight; **CHILD** 15 mg/kg as a loading dose at rate of 1 mg/kg/minute (not exceeding 50 mg/minute); **neonate** 15–20 mg/kg as a
loading dose at rate of 1–3 mg/kg/minute

**DILUTION AND ADMINISTRATION.**

According to manufacturer’s directions

**Adverse effects:**

- gastric intolerance, headache, sleeplessness, agitation (during initial phase); sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, slurred speech, cerebellar-vestibular symptoms, behavioural disorders, hallucinations, hyperglycaemia (may be signs of overdosage); gingival hyperplasia, acne, coarse facies, hirsutism, fever, hepatitis, neurological changes (peripheral neuropathy, choreiform movements, impaired cognition, increased seizure frequency); osteomalacia, rickets (associated with reduced plasma calcium levels); lymph-node enlargement; rashes (discontinue; if mild reintroduce cautiously, but discontinue if recurrence); very rarely, Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, toxic epidermal necrolysis; rarely blood disorders including megaloblastic anaemia (may be treated with folic acid), leukopenia, thrombocytopenia, agranulocytosis with or without bone marrow depression; intravenous administration—cardiovascular and CNS depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, alterations in respiratory function (including respiratory collapse)

**SODIUM VALPROATE**

**Gastro-resistant tablets** (Enteric-coated tablets) 200mg or sodium valproate 250 mg; 500mg

**Uses:**

- Generalized tonic-clonic seizures; partial seizures; atonic seizures; absence seizures; myoclonic seizures; acute mania (section 24.2.2)

**Contraindications:**

- Active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria

**Precautions:**

- monitor liver function before and during first 6 months of therapy (Appendix 5), 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 (Appendix 4); pregnancy (important see notes above; Appendix 2 (neural tube screening)); breastfeeding (see notes above; Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal;

interactions: Appendix 1

**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

**Dosage:**
Generalized tonic-clonic seizures, partial seizures, absence seizures, atonic seizures; myoclonic seizures, by mouth, ADULT initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily at 3-day intervals to maximum of 2.5 g daily in divided doses; usual maintenance dose 1–2 g daily (20–30 mg/kg daily); CHILD up to 20 kg, initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations monitored (above 40 mg/kg daily also monitor clinical chemistry and haematological parameters); CHILD over 20 kg, initially 400 mg daily in divided doses, increased until control (usually in range of 20–30 mg/kg daily); maximum 35 mg/kg daily

**NOTE.**
Plasma concentrations in therapeutic range of 40–100 mg/litre (280 to 700 micromol/litre); not generally considered useful in assessing control, but higher levels associated with increased incidence of adverse effects; indicator of compliance, dose change or co-medication

**Adverse effects:**
Gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (see Precautions—withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness or loss of seizure control); sedation reported and also increased alertness; behavioural disturbances; rarely pancreatitis (measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema...
multiforme), vasculitis, hirsutism and acne reported

**Lamotrigine (SAD)**

*Tablets, 25mg*

**Use**

Monotherapy and adjunctive treatment of partial seizures and primary and secondary generalised tonic-clonic seizures; seizures associated with Lennox-Gastaut syndrome

**Adverse effects**

Skin rashes, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, especially in children, and usually occur within 8 weeks of starting lamotrigine; fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy, and facial oedema and, rarely, hepatic dysfunction, leucopenia, thrombocytopenia; angioedema and photosensitivity; diplopia, blurred vision, and conjunctivitis; and dizziness, drowsiness, insomnia, headache, ataxia, nystagmus, tremor, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion.

**Precautions**

Lamotrigine should be given with caution to patients with hepatic or renal impairment. Patients receiving lamotrigine should be closely monitored, especially for changes in hepatic, renal, and clotting functions. Children’s body-weight should also be monitored and the dose reviewed if necessary. All patients should be warned to see their doctor immediately if rashes or flu-like symptoms associated with hypersensitivity develops. To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. Particular care is needed in patients also receiving valproate. Withdrawal of lamotrigine should be considered if rash, fever, flu-like symptoms, drowsiness, or worsening of seizure control occurs. Abrupt withdrawal should be avoided unless serious skin reactions have occurred.

**Dosage**

The initial **ADULT** dose for use as *monotherapy* is 25 mg once daily by mouth for 2 weeks followed by 50 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 50 to 100 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily, given as a single dose or in 2 divided doses. Some patients have required up to 500 mg daily.

The initial adult dose of lamotrigine for use as an **adjunct** to therapy with enzyme-inducing antiepileptics (but **not with valproate**) is 50 mg once daily for 2 weeks followed by 50 mg twice daily for 2 weeks; thereafter the dose is increased by a maximum of 100 mg every 1 to 2 weeks to usual maintenance doses of 200 to 400 mg daily given in 2 divided doses. Some patients have required up to 700 mg daily.

In adults **taking valproate** the initial dose of lamotrigine is 25 mg.
every other day for 2 weeks followed by 25 mg once daily for 2 weeks; thereafter the dose is increased by a maximum of 25 to 50 mg every 1 to 2 weeks to usual maintenance doses of 100 to 200 mg daily given as a single dose or in 2 divided doses. The doses above are also permitted in CHILDREN over 12 years of age; the use of lamotrigine as monotherapy is not recommended for children under 12 years of age.

For children aged 2 to 12 years the initial dose of lamotrigine as an adjunct to therapy with enzyme-inducing antiepileptics (but not with valproate) is 600 micrograms/kg daily in 2 divided doses for 2 weeks followed by 1.2 mg/kg daily in 2 divided doses for 2 weeks; thereafter the dose is increased by a maximum of 1.2 mg/kg every 1 to 2 weeks to usual maintenance doses of 5 to 15 mg/kg daily given in 2 divided doses.

In children taking valproate, the initial dose of lamotrigine is 150 micrograms/kg once daily for 2 weeks followed by 300 micrograms/kg once daily for 2 weeks; thereafter the dose is increased by a maximum of 300 micrograms/kg every 1 to 2 weeks to usual maintenance doses of 1 to 5 mg/kg, which may be given once daily or in 2 divided doses.

If the calculated dose for children lies between 1 and 2 mg then 2 mg may be given on alternate days for the first 2 weeks of therapy. Lamotrigine should not be administered if the calculated dose is less than 1 mg.

If the potential for interaction with adjunctive antiepileptics is unknown, treatment with lamotrigine should be started with lower doses such as those used with valproate.

In the management of bipolar disorder, the target dose of lamotrigine is 200 mg daily as monotherapy; for patients taking valproate the target dose is 100 mg daily and in those taking enzyme-inducing drugs (but not with valproate) the target dose is 400 mg daily. Lamotrigine should be started at a reduced dose and increased gradually to the target dose in a regimen similar to that used in the treatment of epilepsy. Doses should be reduced in patients with hepatic impairment regardless of indication.
5.1 Control of epilepsy

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SECTION 6: ANTI-INFECTIVE DRUGS

6.1 Antihelminthics
6.2 Antibacterials
6.3 Antifungal medicines
6.4 Antivirals
6.5 Antiprotozoals
6.1 Anthelminthics

Intestinal anthelminthics

Cestode infections

Cestode infections (tapeworms) include intestinal taeniasis and cysticercosis, hymenolepiasis (dwarf tapeworm), diphyllobothriasis and echinococcosis (hydatid disease). Cysticercosis is a systemic infection caused by the larval form (cysticercus) of *Taenia solium*.

Neurocysticercosis occurs when the infection involves the brain. In man, echinococcosis is due to the larval stage of *Echinococcus granulosus* or *E. multilocularis*. The larvae (oncospheres) develop by expansion (cystic echinococcosis) or tumour-like infiltration (alveolar echinococcosis), respectively, in the liver, lungs, or other organs.

**DIPHYLLOBOTHRIASIS**

In diphyllobothriasis, *niclosamide* in a single dose is highly effective. Hydroxocobalamin and folic acid supplements may also be required.

**ECHINOCOCCOSIS**

In echinococcosis, surgery (or, if this is not possible, a technique such as 'puncture-aspiration-injection-reaspiration') is the treatment of choice for operable cystic disease due to *Echinococcus granulosus* but chemotherapy with benzimidazoles, such as *albendazole*, may be of value as adjunctive therapy. Alveolar echinococcosis due to *E. multilocularis* requires both surgery and long-term treatment with either mebendazole or albendazole to inhibit spread of the infection.

In *animal* studies, albendazole and mebendazole have been found to be teratogenic. They are contraindicated for the treatment of cestode infections in pregnancy; pregnancy should be excluded before treatment with albendazole (non-hormonal contraception during and for 1 month after treatment). For single-dose or short-term use in pregnancy, see section 6.1.1.2.

**ALBENDAZOLE**
Chewable tablets, albendazole 400 mg

Uses:
Echinococcus multilocularis and E. granulosus infections prior to or not amenable to surgery; neurocysticercosis; nematode infections (sections 6.1.1.2 and 6.1.1.3); filariasis (section 6.1.2.2)

Contraindications:
Pregnancy (Appendix 2; see notes above and Precautions)

Precautions:
Liver function tests and blood counts before treatment and twice during each cycle; exclude pregnancy before starting treatment (non-hormonal contraception during and for 1 month after treatment); breastfeeding; interactions: Appendix 1

Dosage:
Cystic echinococcosis, by mouth, ADULT over 60 kg, 800 mg daily in 2 divided doses for 28 days followed by 14 tablet-free days; ADULT less than 60 kg, 15 mg/kg daily in two divided doses (to a maximum daily dose of 800 mg) for 28 days followed by 14 tablet-free days; up to 3 courses may be given
Alveolar echinococcosis, by mouth, ADULT as for cystic echinococcosis, but treatment cycles may need to be continued for months or years
Neurocysticercosis, by mouth, ADULT over 60 kg, 800 mg daily in 2 divided doses for 8–30 days; ADULT less than 60 kg, 15 mg/kg daily in two divided doses (to a maximum daily dose of 800 mg) for 8–30 days

Adverse effects:
gastrointestinal disturbances, headache, dizziness; increases in liver enzymes; reversible alopecia; rash; fever; leukopenia and rarely, pancytopenia; allergic shock if cyst leakage; convulsions and meningism in cerebral disease
ed liver enzymes, alopecia, bone marrow depression

NICLOSAMIDE

Chewable tablets, niclosamide 500 mg

Uses:
Taenia saginata, T. solium, Hymenolepis nana, and Diphyllobothrium latum infections

Precautions:
Chronic constipation (restore regular bowel movement before treatment); give antiemetic before treatment; not effective against larval worms; pregnancy (Appendix 2)

Dosage:
Taenia solium infection, by mouth, ADULT and CHILD over 6 years 2 g as a single dose after a light breakfast, followed by a purgative after 2 hours; CHILD under 2 years 500 mg,
2–6 years 1 g
*T. saginata* and *Diphyllobothrium latum* infections, *by mouth*, as for *T. solium* but half the dose may be taken after breakfast and the remainder 1 hour later followed by a purgative 2 hours after last dose

*Hymenolepis nana* infection, *by mouth*, ADULT and CHILD over 6 years 2 g as a single dose on first day then 1 g daily for 6 days; 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

**Patient Advice.**

Tablets should be chewed thoroughly (or crushed) before washing down with water

**Adverse effects:**

Nausea, retching, abdominal pain; lightheadedness; pruritus

*Diphyllobothrium latum* infection, *by mouth*, ADULT and CHILD over 4 years, 10–25 mg/kg as a single dose

Cysticercosis, *by mouth*, ADULT and CHILD over 4 years, 50 mg/kg daily in 3 divided doses for 14 days with prednisolone (or similar corticosteroid) given 2–3 days before and throughout treatment period

Dermal cysticercosis, *by mouth*, ADULT and CHILD over 4 years, 60 mg/kg daily in 3 divided doses for 6 days

**Adverse effects:**

Abdominal discomfort, nausea, vomiting, diarrhoea, malaise; headache, dizziness, drowsiness; rarely hypersensitivity reactions including fever, urticaria, pruritus, eosinophilia (may be due to dead and dying parasites); in neurocysticercosis, headache, hyperthermia, seizures, intracranial hypertension (inflammatory response to dead and dying parasites in CNS)

**Intestinal nematode infections**

Intestinal nematode infections include ascariasis, capillariasis, enterobiasis, hookworm infection, strongyloidiasis, trichostongyliasis and trichuriasis.

**ASCARIASIS**

Ascariasis is an infection, usually of the small intestine, caused by *Ascaris lumbricoides* (roundworm). Broad-spectrum anthelminthic, *albendazole* is effective in the treatment of this infection.

**CAPILLARIASIS**

Capillariasis is caused by infection of the intestine with *Capillaria philippinensis*. Prolonged treatment with *albendazole* offers the only prospect of cure.
ENTEROBIASIS

Enterobiasis is an infection of the large intestine caused by *Enterobius vermicularis* (pinworm, threadworm). All household members should be treated concurrently with a single dose of **mebendazole**, **albendazole** or **pyrantel**. Since reinfection readily occurs, at least one further dose should be given 2–4 weeks later. Piperazine is also effective but must be taken regularly for at least 7 consecutive days.

HOOKWORM INFECTIONS

Hookworm infections are caused by *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis); they are a major cause of iron-deficiency anaemia in the tropics and sub-tropics. Ideally all cases of hookworm infection should be treated. However, when this is impracticable, priority should be given to women in second- and third-trimester of pregnancy, children and debilitated patients. In hookworm, broad-spectrum anthelminthics are preferred wherever other nematode infections are endemic. Both **mebendazole** and **albendazole** are effective.

In animal studies, **albendazole** and **mebendazole** have been found to be teratogenic. There is some evidence to suggest that the use of mebendazole in pregnancy is not associated with an increased incidence of adverse effects on the fetus. However, neither mebendazole nor albendazole should be used during the first trimester of pregnancy to treat nematode infections. Both drugs are contraindicated for the treatment of cestode infections in pregnancy (see section 6.1.1.1).

**Levamisole** is effective in the treatment of mixed *Ascaris* and hookworm infections and **pyrantel** has been highly effective in some community-based control programmes, although several doses are often needed to eliminate *Necator americanus* infection. Patients with iron-deficiency anaemia caused by hookworm infection require supplementary iron salts and should receive ferrous sulfate (200 mg daily for adults) for at least 3 months after the haemoglobin concentration of 12 g/100 ml is obtained.

STRONGYLOIDIASIS

Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis*. All infected patients should be treated. **Ivermectin** in a single dose of 200 micrograms/kg or 200 micrograms/kg/day on two consecutive days is the treat-
ment of choice for chronic strongyloidiasis but it may not be available in all countries. Albendazole 400 mg once or twice daily for 3 days is well tolerated by both adults and children aged over 2 years and it may eradicate up to 80% of infections. Mebendazole has also been used but, to be effective, it must be administered for longer periods as it has a limited effect on larvae and hence the prevention of autoinfection.

TRICHOSTRONGYLIASIS

Trichostongyliasis is an infection of the small intestine caused by Trichostrongylus spp. In symptomatic trichostongyliasis, a single dose of pyrantel (10 mg/kg) or albendazole (400 mg) is effective.

TRICHRURIASIS

Trichuriasis is an infection of the large intestine caused by Trichuris trichiura (whipworm). Chemotherapy is required whenever symptoms develop or when faecal samples are found to be heavily contaminated (up to 10 000 eggs per gram). A single dose of albendazole (400 mg) or mebendazole (500 mg) can be effective in mild to moderate infections; heavier infections require a 3-day course.

ALBENDAZOLE

Chewable tablets, albendazole 400 mg

Uses:
ascariasis, hookworm infections, strongyloidiasis, enterobiasis, trichuriasis, trichostongyliasis, and capillariasis; cestode infections (section 6.1.1.1); tissue nematode infections (section 6.1.1.3); filariasis (6.1.2.2)

Precautions:
pregnancy (see notes above and Appendix 2; also section 6.1.1.1); interactions: Appendix 1

Dosage:
Ascariasis, hookworm infections, enterobiasis, and trichostongyliasis, by mouth, ADULT and CHILD over 2 years, 400 mg as a single dose; child 12 months–2 years, 200 mg as a single dose
Trichuriasis, by mouth, ADULT and CHILD over 2 years, 400 mg as a single dose (for moderate infections) or 400 mg daily for 3 days (severe infections); child 12 months–2 years, 200 mg as a single dose (for moderate infections) or 200 mg initially then 100 mg twice daily for 3 days (severe infections)
Strongyloidiasis, by mouth, ADULT and CHILD over 2 years, 400 mg once or twice daily for 3 days
Capillariasis, by mouth, ADULT and CHILD over 2 years, 400 mg daily for 10 days

**Adverse effects:**
gastrointestinal discomfort, headache; adverse effects associated with use in cestode infections (section 6.1.1.1)

## 6.2 Antibacterials

### Beta-lactam drugs

Beta-lactam antibiotics including penicillins, cefalosporins and carbapenems share a common structure; they are bactericidal, their mechanism of action resulting from inhibition of peptidoglycan, a mucopentide in bacterial cell walls. Benzylpenicillin and phenoxyethylpenicillin are active against susceptible strains of Gram-positive bacteria and Gram-negative bacteria, spirochaetes, and actinomycetes, but are inactivated by penicillinase and other beta-lactamases. Benzathine benzylpenicillin and procaine benzylpenicillin are long-acting preparations which slowly release benzylpenicillin on injection. A range of penicillins with improved stability to gastric acid and penicillinases have been produced by substitution of the 6-amino position of 6-aminopenicillanic acid. Cloxacillin is an isoxazoyl penicillin which is resistant to staphylococcal penicillinase. Broad-spectrum penicillins such as ampicillin are acid-stable and active against Gram-positive and Gram-negative bacteria, but are inactivated by penicillinase. Beta-lactamase inhibitors such as clavulanic acid are often necessary to provide activity against beta-lactamases produced by a wide range of both Gram-negative and Gram-positive bacteria.

Cefalosporins are classified by generation, with the first generation agents having Gram-positive and some Gram-negative activity; the second generation drugs have improved Gram-negative activity and the third generation cefalosporins have a wider spectrum of activity, although may be less active against Gram-positive bacteria than first generation drugs, but they are active against Gram-negative Enterobacteriaceae and Pseudomonas aeruginosa.

Carbapenems are semisynthetic derivatives of Streptomyces cattleya. They have a broad spectrum of activity and are stable to most penicillinas. They should be reserved for severe infections resistant to other antibiotics.

Penicillins may cause encephalopathy due to cerebral irritation. This rare, but serious adverse effect may result from very high doses or in severe renal failure. Penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.
HYPERSENSITIVITY

The most important adverse effect of penicillins is hypersensitivity which causes rashes and, occasionally anaphylaxis, which can be fatal. A careful history should be taken with regard to previous allergic reactions. If rash develops, another antimicrobial should be substituted. Allergic reactions to penicillins occur in 1–10% of exposed individuals, while anaphylactic reactions occur in fewer than 0.05% of treated patients. Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin. These individuals should not receive a penicillin, a cefalosporin or another beta-lactam antibiotic. Patients who are allergic to one penicillin will be allergic to them all because the hypersensitivity is related to the basic penicillin structure and about 10% 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 and in these individuals a penicillin should not be withheld unnecessarily for a serious infection; however, the possibility of an allergic reaction should be borne in mind and facilities should be available for treating anaphylaxis.

Benzylpenicillins and phenoxyethylpenicillin

Benzylpenicillin remains an important and useful antibiotic but it is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal and meningococcal infections and also for anthrax, diphtheria, gas gangrene, leptospirosis, tetanus and treatment of Lyme disease in children. Pneumococci, meningococci and gonococci often have decreased sensitivity to penicillin and benzylpenicillin is no longer the first choice for pneumococcal meningitis. Benzylpenicillin is given by injection as it is inactivated by gastric acid and absorption from the intestinal tract is low. Depot preparations are used when therapeutic concentrations need to be sustained for several hours. Benzathine benzylpenicillin or procaine benzylpenicillin provides a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. They are the preferred choice for the treatment of syphilis or yaws.

Phenoxyethylpenicillin is suitable for oral administration; it has a similar spectrum of activity but is less effective than benzylpenicillin. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable.
BENZYL PENICILLIN

Penicillin G

*Injection* (Powder for solution for injection), benzylpenicillin sodium 600-mg vial (1 million units), 3-g vial (5 million units)

**Uses:**
- pneumonia; throat infections; otitis media; Lyme disease in children; streptococcal endocarditis; meningococcal disease; necrotizing enterocolitis; necrotizing fasciitis; leptospirosis; neurosyphilis; anthrax; actinomycosis; brain abscess; gas gangrene; cellulitis; osteomyelitis

**Contraindications:**
- Penicillin hypersensitivity (see notes above); avoid intrathecal route (see notes above)
- History of allergy (see notes above); renal failure (Appendix 4); heart failure; pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

**Precautions:**
- History of allergy (see notes above); renal failure (Appendix 4); heart failure; pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

**Dosage:**
- Mild to moderate infections due to sensitive organisms, *by intramuscular injection or by slow intravenous injection or by intravenous infusion*, **ADULT** 0.6–2.4 g daily in 2–4 divided doses, with higher doses in severe infections and duration of treatment depending on disease (see also below); **neonate** 50 mg/kg daily in 2 divided doses; **infant** 1 to 4 weeks, 75 mg/kg daily in 3 divided doses; **CHILD** 1 month to 12 years, 100 mg/kg daily in 4 divided doses, with higher doses in severe infections (see also below)
- Bacterial endocarditis, *by slow intravenous injection or by intravenous infusion*, **ADULT** up to 7.2 g daily in 6 divided doses
- Meningococcal disease, *by slow intravenous injection or by intravenous infusion*, **ADULT** up to 14.4 g daily in divided doses; **premature infant** and **neonate** 100 mg/kg daily in 2 divided doses; **infant** 150 mg/kg daily in 3 divided doses; **CHILD** 1 month to 12 years, 180–300 mg/kg daily in 4–6 divided doses
- Suspected meningococcal disease (before transfer to hospital), *by intramuscular injection or by slow intravenous injection*, **ADULT** and **CHILD** over 10 years, 1.2 g; **CHILD** under 1 year, 300 mg; **CHILD** 1 to 9 years, 600 mg
- Neurosyphilis, *by slow intravenous injection*, **ADULT** 1.8–2.4 g every 4 hours for 2 weeks
- Congenital syphilis, *by intramuscular injection or by slow intravenous injection*, **CHILD** up to 2 years, 30 mg/kg daily in 2 divided doses for 10 days; **CHILD** over 2 years, 120–180 mg/kg (to a maximum of 1.44 g) daily in divided doses for 14 days

**RECONSTITUTION AND ADMINISTRATION.**

According to manufacturer’s directions

**Adverse effects:**

hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); diarrhoea, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders, central nervous system toxicity, including convulsions, coma, and encephalopathy (associated with high dosage, or severe renal failure); electrolyte disturbances; Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins); inflammation, phlebitis or thrombophlebitis at injection sites

**BENZATHINE BENZYLPPENICILLIN**

*Injection* (Powder for solution for injection), benzathine benzylpenicillin, 1.8-g vial (equivalent to benzylpenicillin 1.44 g, 2.4 million units)

**Uses:**

Streptococcal pharyngitis; diphtheria carrier state; syphilis and other treponemal infections (yaws, pinta, bejel); rheumatic fever prophylaxis

**Contraindications:**

Penicillin hypersensitivity (see notes above); intravascular injection; neurosyphilis

**Precautions:**

History of allergy (see notes above); renal failure (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

**Dosage:**

Streptococcal pharyngitis; primary prophylaxis of rheumatic fever, *by deep intramuscular injection*, ADULT and CHILD over 30 kg, 900 mg as a single dose; CHILD under 30 kg, 450–675 mg as a single dose

Secondary prophylaxis of rheumatic fever, *by deep intramuscular injection*, ADULT and CHILD over 30 kg, 900 mg once every 3–4 weeks; CHILD under 30 kg, 450 mg once every 3–4 weeks

Early syphilis, *by deep intramuscular injection*, ADULT 1.8 g as a single dose, divided between 2 sites

Late syphilis, *by deep intramuscular injection*, ADULT 1.8 g, divided between two sites, once weekly for 3 consecutive weeks

Congenital syphilis (where no evidence of CSF involvement), *by deep intramuscular injection*, CHILD up to 2 years, 37.5...
mg/kg as a single dose
Yaws, pinta, and bejel, by deep intramuscular injection, ADULT
900 mg as a single dose; CHILD 450 mg as a single dose

RECONSTITUTION AND ADMINISTRATION.
According to manufacturer’s directions

Adverse effects
hypersensitivity reactions including urticaria, fever, joint
pains, rashes, angioedema, anaphylaxis, serum sickness-like
reaction, haemolytic anaemia, interstitial nephritis (see also
notes above); neutropenia, thrombocytopenia, coagulation
disorders and central nervous system toxicity (associated
with high dosage or severe renal failure); Jarisch-Herxheimer
reaction (during treatment for syphilis and other spirochaete
infections, probably due to release of endotoxins); rarely,
non-allergic (embolic-toxic) reactions; pain and inflammation
at injection site

PROCAINE BENZYLPERCILLIN

Injection (Powder for solution for injection), procaine benzylpenicillin 1-g vial (1 million units), 3-g vial (3 million units)

Uses
Syphilis; anthrax; childhood pneumonia; diphtheria carrier state;
cellulitis; mouth infections; bites

Contraindications
Hypersensitivity to penicillins (see notes above); intravascular
injection

Precautions
History of allergy (see notes above); renal failure (Appendix
4); interactions: Appendix 1

Dosage
Infections due to sensitive organisms, by deep intramuscular
injection ADULT 0.6 to 1.2 g daily
Pneumonia, by deep intramuscular injection, CHILD 50 mg/
kg daily for 10 days
Syphilis, by deep intramuscular injection, ADULT 1.2 g daily
for 10 to 15 days, or up to 3 weeks in late syphilis
Congenital syphilis, by deep intramuscular injection, CHILD
up to 2 years, 50 mg/kg daily for 10 days

RECONSTITUTION AND ADMINISTRATION.
According to manufacturer’s directions

Adverse effects:
hypersensitivity reactions including urticaria, fever, joint pains,
rashes, angioedema, anaphylaxis, serum sickness-like reac-
tion, haemolytic anaemia, interstitial nephritis (see also notes
above); neutropenia, thrombocytopenia, coagulation disorders
and central nervous system toxicity (associated with high doses
and severe renal failure); Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins); rarely, non-allergic (embolic-toxic) reactions; pain and inflammation at injection site

**PHENOXYMETHYLPENICILLIN**

**Penicillin V**

*Tablets*, phenoxyethylpenicillin (as potassium salt) 250 mg

*Oral suspension* (Powder for oral suspension), phenoxyethylpenicillin (as potassium salt) 250 mg/5 ml

**Uses:**

Streptococcal pharyngitis; otitis media; erysipelas; mouth infections; secondary prophylaxis of rheumatic fever; post-splenectomy prophylaxis

**Contraindications:**

Hypersensitivity to penicillins (see notes above); serious infections (see notes above)

**Precautions:**

History of allergy (see notes above); pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

**Dosage**

Infections due to sensitive organisms, *by mouth*, **ADULT** 500 mg every 6 hours increased up to 1 g every 6 hours in severe infections; **CHILD** up to 1 year, 62.5 mg every 6 hours; **CHILD** 1–5 years, 125 mg every 6 hours; **CHILD** 6–12 years, 250 mg every 6 hours

Secondary prophylaxis of rheumatic fever, *by mouth*, **ADULT** 500 mg twice daily; **CHILD** 1–5 years, 125 mg twice daily; **CHILD** 6–12 years, 250 mg twice daily

**Patient Advice.** Phenoxyethylpenicillin should be taken at least 30 minutes before or 2 hours after food

**Adverse effects**

Hypersensitivity reactions including urticaria, joint pain, rash, angioedema, anaphylaxis (see notes above); nausea and diarrhoea

**Ampicillin, amoxicillin, amoxicillin with clavulanic acid and cloxacillin**

**Ampicillin** is active against certain Gram-positive and Gram-negative organisms. It is used to treat a wide range of infections including otitis media, respiratory-tract and urinary-tract infections, and gonorrhoea due to susceptible bacteria. However, ampicillin is inactivated by penicillinases including those produced by *Staphylococcus aureus* and by common Gram-negative bacilli such as *Escherichia coli*; many strains
of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, and *Salmonella* and *Shigella* spp. are resistant. There are geographical variations in the incidence of resistance and an awareness of local patterns is important. In some areas, oral use should be restricted to treatment of *Shigella* infections; it is given in an oral dose of 1 g every 6 hours for 7–10 days.

**Amoxicillin** has a similar spectrum of activity to ampicillin, but is also inactivated by penicillinases. However, it is better absorbed after oral administration than ampicillin and higher plasma and tissue levels are achieved. Amoxicillin is preferred to ampicillin for the treatment of some infections including otitis media and respiratory-tract and urinary-tract infections.

**Clavulanic acid** is a beta-lactamase inhibitor. It has no significant antibacterial activity but in combination with **amoxicillin** widens amoxicillin’s spectrum of activity and allows its use against amoxicillin-resistant strains of bacteria. It is used in respiratory-tract, genito-urinary and abdominal infections, cellulitis, animal bites, and dental infections.

**Cloxacillin** is used to treat infections due to penicillinase-producing staphylococci which are resistant to benzylpenicillin. It is acid-stable and may therefore be given by mouth as well as by injection.

These antibiotics may also be administered with an aminoglycoside to increase their spectrums of activity. The penicillin and aminoglycoside should not be mixed before or during administration, because loss of aminoglycoside activity can occur on mixing.

**AMOXICILLIN**

**Capsules**, amoxicillin 250 mg, 500 mg

**Oral suspension** (Powder for oral suspension), amoxicillin 125 mg/5 ml

**Uses**

urinary-tract infections, upper respiratory-tract infections, bronchitis; pneumonia; otitis media; dental abscess; osteomyelitis; Lyme disease in children; endocarditis prophylaxis; post-splenectomy prophylaxis; gynaecological infections; gonorrhoea; *Helicobacter pylori* eradication (section 17.1)

**Contraindications**

Hypersensitivity to penicillins (see notes above)

**Precautions**

History of allergy (see notes above); renal impairment (Appendix 4); erythematous rashes common in glandular fever, chronic lymphatic leukaemia, and possibly HIV infection; pregnancy and breastfeeding (Appendices 2 and 3); interac-

Dosage
Infections due to sensitive organisms, by mouth, ADULT and CHILD over 10 years, 250 mg every 8 hours, doubled in severe infections; CHILD up to 10 years, 125 mg every 8 hours, doubled in severe infections
Severe or recurrent purulent respiratory-tract infections, by mouth, ADULT 3 g every 12 hours
Pneumonia, by mouth, adult 0.5–1 g every 8 hours
Dental abscess (short course), by mouth, ADULT 3 g repeated once after 8 hours
Urinary-tract infections (short course), by mouth, ADULT 3 g repeated once after 10–12 hours
Chlamydia, by mouth, 500 mg every 8 hours for 7 days
Gonorrhoea (short course), by mouth, ADULT 3 g as a single dose (with probenecid 1 g)
Otitis media (short course), by mouth, CHILD aged 3–10 years, 750 mg twice daily for 2 days

Adverse effects
nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response; may be serious reaction—discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; rarely, central nervous system disorders including convulsions associated with high doses or impaired renal function

AMOXICILLIN WITH CLAVULANIC ACID

Tablets, amoxicillin (as trihydrate) 500 mg with clavulanic acid (as potassium salt) 125 mg
Oral suspension (Powder for oral suspension), amoxicillin (as trihydrate) 125 mg with clavulanic acid (as potassium salt) 31.25 mg

Uses
Infections due to beta-lactamase producing bacteria (where amoxicillin alone not appropriate) including respiratory-tract infections, genito-urinary and abdominal infections, cellulitis, animal bites, severe dental infections, and surgical prophylaxis

Contraindications
Hypersensitivity to penicillins (see notes above); history of penicillin- or amoxicillin with clavulanic acid-associated jaundice or hepatic dysfunction

Precautions
history of allergy (see notes above); renal impairment (Appendix 4); erythematous rashes common in glandular
fever, chronic lymphatic leukaemia, and possibly HIV infection; hepatic impairment (Appendix 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage

NOTE.
All doses expressed as amoxicillin

Infections due to susceptible beta-lactamase producing organisms, by mouth, ADULT and CHILD over 12 years, 250 mg every 8 hours, doubled in severe infections; CHILD under 1 year, 20 mg/kg daily in 3 divided doses; 1–6 years, 125 mg every 8 hours; 6–12 years, 250 mg every 8 hours

Severe dental infections, by mouth, ADULT 250 mg every 8 hours for 5 days

Infections due to susceptible beta-lactamase producing organisms, by intravenous injection over 3–4 minutes, ADULT and CHILD over 12 years, 1 g every 8 hours, increased to 1 g every 6 hours in severe infections; neonate and premature infant 25 mg/kg every 12 hours; infant up to 3 months, 25 mg/kg every 8 hours; CHILD 3 months to 12 years, 25 mg/kg every 8 hours increased to 25 mg/kg every 6 hours in more severe infections

Surgical prophylaxis, by intravenous injection, ADULT 1 g at induction, with up to 2–3 further doses of 1 g every 8 hours if increased risk of infection)

RECONSTITUTION AND ADMINISTRATION.

According to manufacturer’s directions

Adverse effects

nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response—may be serious, discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-type reaction, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; dizziness, headache, convulsions (particularly with high doses or in renal impairment); hepatitis, cholestatic jaundice; erythema multiforme (including Stevens-Johnson syndrome), toxic epidermal necrolysis, exfoliative dermatitis, vasculitis reported; superficial staining of teeth with suspension; phlebitis at injection site

AMPICILLIN

Injection (Powder for solution for injection), ampicillin (as sodium salt) 500-mg vial, 1-g vial

Uses

mastoiditis; gynaecological infections; sepsicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis

Contraindications

Hypersensitivity to penicillins (see notes above)

**Precautions**
History of allergy (see notes above); renal impairment (Appendix 4); erythematous rashes common in glandular fever, acute or chronic lymphocytic leukaemia, and cytomegalovirus infection; pregnancy and breastfeeding (Appendices 2 and 3);

**interactions:** Appendix 1

**Dosage**
Severe infections due to sensitive organisms, by intramuscular, by slow intravenous injection or by intravenous infusion,

**ADULT** 500 mg every 4–6 hours; **CHILD** under 10 years, half the adult dose

Meningitis, by slow intravenous injection, **ADULT** 1–2 g every 3–6 hours (maximum 14 g daily); **CHILD** 150–200 mg/kg daily in divided doses

Listerial meningitis (in combination with another antibacterial), by intravenous infusion, **adult** 2 g every 4 hours for 10–14 days; **infant** under 1 month, 50 mg/kg every 6 hours; 1–3 months, 50–100 mg/kg every 6 hours; **child** 3 months–12 years, 100 mg/kg every 6 hours (maximum 12 g daily)

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects**
nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response—may be serious reaction, discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders

**CLOXACILLIN**
Cloxacillin is representative penicillinase-resistant penicillin. Various drugs such as dicloxacillin can serve as alternatives

**Capsules**, cloxacillin (as sodium salt) 500 mg

**Oral solution** (Powder for oral solution), cloxacillin (as sodium salt) 125 mg/5 ml

**Injection** (Powder for solution for injection), cloxacillin (as sodium salt) 500-mg vial

**Uses:**
Infections due to beta-lactamase-producing staphylococci including impetigo, cellulitis and other soft-tissue infections; staphylococcal endocarditis, septicaemia, pneumonia and osteomyelitis

**Contraindications:**
Hypersensitivity to penicillins (see notes above)

**Precautions:**

History of allergy (see notes above); renal and hepatic impairment (Appendices 4 and 5); heart failure; pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

Dosage:
Infections due to susceptible beta-lactamase-producing staphylococci, by mouth, ADULT 500 mg 4 times daily, doubled in severe infection; by intramuscular injection, 250 mg every 4–6 hours, doubled in severe infection; by slow intravenous injection or intravenous infusion, 1–2 g every 6 hours; CHILD up to 2 years, quarter adult dose; CHILD 2–10 years, half adult dose

RECONSTITUTION AND ADMINISTRATION.
According to manufacturer’s directions

Adverse effects:
nausea and vomiting, diarrhoea; hypersensitivity reactions including urticaria, fever, joint pain, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopenia, coagulation disorders; antibiotic-associated colitis; hepatitis and cholestatic jaundice—may be delayed in onset; electrolyte disturbances; pain, inflammation, phlebitis or thrombophlebitis at injection sites

Cefalosporins and imipenem with cilastatin

The cephalosporins are broad—spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis and urinary-tract-infections

Cefuroxime is a second generation cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases. It is therefore active against certain bacteria which are resistant to the other drugs and has greater activity against Haemophilus influenzae and Neisseria gonorrhoeae.

Cefazidime, ceftriaxone and cefotaxime are third generation cefalosporins with greater activity than the second generation cephalosporins against certain Gram-negative bacteria. Ceftriaxone is used for serious infections such as septicaemia, pneumonia and meningitis; it is used as a reserve antimicrobial to treat meningitis due to Streptococcus pneumoniae in some areas where penicillin resistance is found. Cefazidime is active against Pseudomonas aeruginosa and other Gram-negative bacteria; it is used in the treatment of pseudomonas infections and in some areas is restricted to use only where gentamicin resistance is high.

Imipenem is a broad-spectrum antibiotic. As it is partially inactivated by enzymatic activity in the kidney, it is administered with cilastatin which inhibits the renal metabolism of imipenem. It is active against many aerobic and anaerobic Gram-positive and Gram-negative bacteria; in some areas it is reserve agent for the treatment of infections due to Acinetobacter spp. and Ps aeruginosa, which are resistant to other more usual treatments.
CEFTAZIDIME

Ceftazidime is a complementary antibacterial drug for use only when there is significant resistance to other drugs.

Injection (Powder for solution for injection), ceftazidime (as pentahydrate) 250-mg vial

Uses
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); porphyria

Precautions
Penicillin sensitivity (see section 6.2.1); renal impairment (Appendix 4); pregnancy and breastfeeding (but appropriate to use, see Appendices 2 and 3); false positive urinary glucose (if tested for reducing substances) and false positive Coombs’ test; interactions: Appendix 1

Dosage
Infections due to susceptible organisms, by deep intramuscular injection or by intravenous injection or intravenous infusion, ADULT 1 g every 8 hours or 2 g every 12 hours, or in severe infections (including immunocompromised), 2 g every 8–12 hours or 3 g every 12 hours (ELDERLY usual maximum 3 g daily); neonate and infant up to 2 months, 25–60 mg/kg daily in 2 divided doses; CHILD over 2 months, 30–100 mg/kg daily in 2–3 divided doses (intravenous route recommended for children)

Pseudomonal lung infection in cystic fibrosis, by deep intramuscular injection or by intravenous injection or intravenous infusion, ADULT with normal renal function, 100–150 mg/kg daily in 3 divided doses

Infections in immunocompromised, cystic fibrosis, or meningitis, by intravenous injection or intravenous infusion, CHILD over 2 months up to 150 mg/kg daily in 3 divided doses (maximum 6 g daily)

Reconstitution and Administration.
According to manufacturer’s directions. Intramuscular doses over 1 g divided between more than one site

Adverse effects
diarrhoea, nausea, vomiting, abdominal discomfort, headache; rarely, antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reaction, fever and arthralgia, and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis, cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible interstitial nephritis; nervousness, sleep disturbances, confu-
sion, hypertonia, and dizziness

**CEFTRIAXONE**

Ceftriaxone is a representative third-generation cefalosporin antibiotic. Various drugs can serve as alternatives. *Injection* (Powder for solution for injection), ceftriaxone (as sodium salt) 250-mg vial

**Uses**

Serious infections due to sensitive bacteria, including sepsis, pneumonia, and meningitis; surgical prophylaxis; prophylaxis of meningococcal meningitis; gonorrhoea

**Contraindications**

Cefalosporin hypersensitivity (see section 6.2.1); porphyria; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding

**Precautions**

Penicillin sensitivity (see section 6.2.1); severe renal impairment (Appendix 4); hepatic impairment if accompanied by renal impairment (Appendix 5); 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; pregnancy and breastfeeding (but appropriate to use, see Appendices 2 and 3); false positive urinary glucose (if tested for reducing substances) and false positive Coombs’ test; *interactions*: Appendix 1

**Dosage**

Infections due to susceptible organisms, *by deep intramuscular injection*, *by intravenous injection* (over at least 2–4 minutes) or *by intravenous infusion*, **ADULT** 1 g daily; severe infections 2–4 g daily; **infant** and **CHILD** under 50 kg 20–50 mg/kg daily; up to 80 mg/kg daily in severe infections (doses of 50 mg/kg and over by intravenous infusion only); *by intravenous infusion* (over 60 minutes), **neonates** 20–50 mg/kg daily (maximum 50 mg/kg daily)

Uncomplicated gonorrhoea, *by deep intramuscular injection*, **ADULT** 125 mg as a single dose

Surgical prophylaxis, *by deep intramuscular injection* or *by intravenous injection* (over at least 2–4 minutes), **ADULT** 1 g at induction

Colorectal surgery (with antibacterial active against anaerobes), *by deep intramuscular injection* or *by intravenous injection* (over at least 2–4 minutes), or *by intravenous infusion*, 2 g as a single dose

**RECONSTITUTION AND ADMINISTRATION.**

According to manufacturer’s directions. Intramuscular doses over 1 g divided between more than one site. Administer by intravenous infusion over 60 minutes in neonates (see also
Cefotaxime

Cefotaxime is a third generation cephalosporin with greater activity than the second generation cephalosporins against certain Gram – negative bacteria.

Injection, powder for reconstitution, cefotaxime (as sodium salt), 1-g vial

Uses
Infections due to sensitive Gram-positive and Gram-negative bacteria, gonorrhoea, surgical prophylaxis, Haemophilus epiglottitis and meningitis

Contra-indications
Cephalosporin hypersensitivity

Precautions
Penicillin sensitivity; renal impairment; pregnancy and breast-feeding (appropriate to use); false positive urinary glucose (if tested for reducing substances) and false positive Coombs’ test

Dose
intramuscular or intravenous injection or by intravenous infusion, 1 g every 12 hours increased in severe infections ( e.g. meningitis) to 8 g daily in 4 divided doses; higher doses (up to 12 g daily in 3-4 divided doses) may be required; NEONATE 50 mg/kg in 2-4 divided doses increased to 150-200 mg/kg in severe infections; CHILD 100-150 mg/kg daily in 2-4 divided doses increased up to 200 mg/kg daily in every severe infections

Gonorrhoea, 500 mg as a single dose

Side-effects
Diarrhea and rarely antibiotic associated colitis, nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, fever, arthralgia, and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; disturbances
in liver enzyme, transient hepatitis and cholestatic jaun-
dice; other side-effects reported include eosinophilia and
blood disorders (including thrombocytopenia, leucopenia,
agranulocytosis, aplastic anaemia and haemolytic anaemia)

Cefuroxime
Cefuroxime is a second generation cephalosporin that is less
susceptible than the earlier cephalosporins to inactivation by
beta-lactamases. It is, therefore, active against certain bacteria
which are resistant to the other drugs and has greater activity
against Haemophilus influenzae and Neisseria gonorrhoeae.
Injection, powder for reconstitution, cefuroxime (as sodium
salt); 750 mg vial
Suspension, cefuroxime (as axetil) 125 mg/5 ml when recon-
stituted with water.
Uses
Infections due to sensitive Gram-positive and Gram-negative
bacteria, surgical prophylaxis; more active against Haemophilus
influenzae and Neisseria gonorrhoeae; Lime disease
Contra-indications:
See under Cefotaxime
Precautions:
See under Cefotaxime
Dosage
Oral, CHILD over 3 months, 125 mg twice daily, if necessary
doubled in child over 2 years with otitis media
By intramuscular or intravenous injection or infusion, 750 mg
every 6-8 hours; 1.5 g every 6-8 hours in severe infections;
single doses over 750 mg intravenous route only.
CHILD usual dose 60 mg/kg daily (range 30-100 mg/kg daily
in 3-4 divided doses (2-3 divided doses in neonates)
ADULTS, Gonorrhoea, 1.5 g as a single dose by intramuscular
injection (divided between two sites)
Surgical prophylaxis, 1.5 g by intravenous injection at induc-
tion; up to 3 further doses of 750 mg may be given by intra-
muscular or intravenous injection every 8 hours for high risk
procedures.
Meningitis, 3 g intravenously every 8 hours; CHILD, 200-240
mg/kg daily (in 3-4 divided doses) reduced to 100 mg/kg daily
after 3 days or on clinical improvement; NEONATE, 100 mg/
kg daily reduced to 50 mg/kg daily
Adverse effects: see under cefotaxime

Cephalexin
Cephalexin is a first-generation cephalosporin
Tablet, cephalexin 250 mg, 500 mg
Oral suspension, cephalexin for reconstitution with water, 125
mg/5ml
Uses
Infections due to sensitive Gram-positive and Gram-negative bacteria

**Contraindications:**
Cephalosporin hypersensitivity

**Precautions:**
Penicillin sensitivity; renal impairment

**Dosage:**
250 mg every 6 hours or 500 mg every 8-12 hours increased to 1-1.5 g every 6-8 hours for severe infection; CHILD 25 mg/kg daily in divided doses, doubled for severe infections, max. 100 mg/kg daily; or under 125 mg every 12 hours, 1-5 years 125 mg every 8 hours, 6-12 years 250 mg every 8 hours

**Adverse effects:**
Nausea and vomiting, abdominal discomfort, headache, allergic reactions including rashes, pruritis, urticaria, serum sickness-like reactions with rashes

**IMIPENEM WITH CILASTATIN. (SAD)**

Imipenem with cilastatin is a complementary antibacterial combination for use only when there is significant resistance to other drugs.

*Injection* (Powder for solution for intramuscular injection), imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg

*Infusion* (Powder for solution for intravenous infusion), imipenem (as monohydrate) 250 mg or 500 mg with cilastatin (as sodium salt) 250 mg or 500 mg, respectively

**Uses**
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**
Hypersensitivity to beta-lactam antibiotics (see section 6.2.1)

**Precautions**
renal impairment (Appendix 4); CNS disorders, such as epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3)

**Dosage**

*NOTE.* All doses are in terms of imipenem

Infections due to susceptible organisms, *by intravenous infusion*, ADULT 1–2 g daily (in 3–4 divided doses); less susceptible organisms, ADULT up to 50 mg/kg daily (maximum 4 g daily) in 3–4 divided doses; CHILD over 3 months, 60 mg/kg daily (maximum 2 g daily) in 4 divided doses; child over 40 kg, adult dose

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer's directions. The intramuscular

preparation must not be administered intravenously. The infusion preparation must not be administered intramuscularly.

**Adverse effects**

- nausea, vomiting, diarrhoea; antibiotic-associated colitis; taste disturbances; tooth or tongue discoloration, hearing loss; blood disorders, positive Coombs’ test; allergic reactions (see section 6.2.1) including rash, pruritus, urticaria, erythema multiforme (Stevens-Johnson syndrome), fever, anaphylactic reactions, rarely toxic epidermal necrolysis, exfoliative dermatitis; myoclonic activity, convulsions, confusion, and mental disturbances; slight increase in liver enzymes and bilirubin, rarely hepatitis; increases in serum creatinine and blood urea; red coloration of urine in children; erythema, pain and induration, and thrombophlebitis at injection sites.

**Other antibacterials**

**Chloramphenicol**

Chloramphenicol is a potent broad-spectrum antibiotic. It is associated with serious haematological adverse effects and should be reserved for the treatment of severe infections, particularly those caused by *Haemophilus influenzae* and typhoid fever. The oily suspension should be reserved for use in situations of catastrophic epidemics of meningococcal meningitis occurring mainly in sub-Saharan Africa, during which the medical services are overwhelmed by the epidemic and in which the overwhelming scale of the epidemic precludes any other form of antimicrobial therapy.

**CHLORAMPHENICOL**

- **Injection** (Powder for solution for injection), chloramphenicol (as sodium succinate) 1-g vial
- **Oily injection** (Suspension for injection), chloramphenicol (as sodium succinate) 500 mg/ml, 2-ml ampoule
- **Eye drops**, 0.5% / 10mls, ointment, 1%

**Uses**

severe life-threatening infections, particularly those caused by *Haemophilus influenzae*, and typhoid fever; also, cerebral abscess; mastoiditis; relapsing fever; gangrene; granuloma inguinale; listeriosis; severe melioidosis; plague; psitticosis; tularaemia; Whipple disease; septicaemia; empirical treatment of meningitis

**Contraindications**

- Pregnancy (Appendix 2); porphyria

**Precautions**

Avoid repeated courses and prolonged use; reduce dose in hepatic impairment (Appendix 5) and severe renal impairment.
6.2 Antibacterials

(Appendix 4); blood counts required before and during treatment; monitor plasma concentrations in neonates (see below); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage

Infections due to susceptible organisms (not susceptible to other antimicrobials), by mouth or by intravenous injection or intravenous infusion, **ADULT** and **CHILD** 50 mg/kg daily in 4 divided doses; up to 100 mg/kg daily in divided doses in severe infections such as meningitis, septicaemia, and haemophilus epiglottitis (reduce high doses as soon as clinically indicated); **infant** under 2 weeks 25 mg/kg daily in 4 divided doses, 2 weeks to 1 year 50 mg/kg daily in 4 divided doses

Epidemics of meningococcal meningitis, by intramuscular injection (of oily injection), **ADULT** 3 g as a single dose, repeated after 48 hours if necessary; **INFANT** 1–8 weeks 250 mg as a single dose, 2–11 months 500 mg as a single dose; **CHILD** 1–2 years 1 g as a single dose, 3–5 years 1.5 g as a single dose, 6–9 years 2 g as a single dose, 10–14 years 2.5 g as a single dose, over 15 years as for adult; dose repeated after 48 hours if necessary

**RECONSTITUTION AND ADMINISTRATION.**

According to manufacturer's directions. The oily injection is for intramuscular use only (see notes above)

**NOTE.**

Plasma concentration monitoring required in neonates and 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) 15–25 mg/litre; pre-dose 'trough' concentration should not exceed 15 mg/litre

Adverse effects:

bone marrow depression—reversible and irreversible aplastic anaemia (with reports of leukaemia), anaemia, leukopenia and thrombocytopenia; nocturnal haemoglobinuria; peripheral neuritis and optic neuritis; nausea, vomiting, diarrhoea, dry mouth, stomatitis, glossitis; headache, depression; hypersensitivity reactions including, rashes, fever, angioedema and rarely anaphylaxis; grey 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

**VANCOMYCIN**

Vancomycin is a complementary antibacterial drug for use only when there is significant resistance to other drugs

**Infusion** (Powder for solution for infusion), vancomycin (as hydrochloride) 250-mg vial

Uses:
methicillin-resistant staphylococcal pneumonia; staphylococcal meningitis; endocarditis prophylaxis (with gentamicin)

Precautions:
avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects); rotate infusion sites; renal impairment (Appendix 4); elderly; history of deafness—avoid; plasma-vancomycin concentration measured after 3 or 4 doses (earlier if renal impairment), blood counts, urinalysis, and renal function tests—use only in hospital setting; monitor auditory function and plasma-vancomycin concentrations in elderly or in renal impairment; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Serious staphylococcal infections, by intravenous infusion, ADULT 500 mg over at least 60 minutes every 6 hours or 1 g over at least 100 minutes every 12 hours; elderly (over 65 years), 500 mg every 12 hours or 1 g once daily; neonate up to 1 week, 15 mg/kg initially, then 10 mg/kg every 12 hours; infant 1–4 weeks, 15 mg/kg initially, then 10 mg/kg every 8 hours; CHILD over 1 month, 10 mg/kg every 6 hours
Endocarditis prophylaxis (for procedures under general anaesthetic), by intravenous infusion, ADULT 1 g over at least 100 minutes then gentamicin 120 mg at induction or 15 minutes before procedure

RECONSTITUTION AND ADMINISTRATION.
According to the manufacturer’s directions
NOTE. Plasma concentration monitoring required; peak plasma concentration (measured 2 hours after infusion) should not exceed 30 mg/litre; pre-dose (trough) concentration should not exceed 5–10 mg/litre

Adverse effects:
nephrotoxicity including renal failure and interstitial nephritis; otoxicity (discontinue if tinnitus occurs); blood disorders; nausea, chills, fever, eosinophilia, anaphylaxis, rashes, including exfoliative dermatitis, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, and vasculitis; phlebitis; on rapid infusion, severe hypotension (with shock, cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ('red man' syndrome), pain and muscle spasm of back and chest

Quinolones

Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against salmonella, shigella, campylobacter, neisseria, Bacillus anthracis and pseudomonas. It is also active against chlamydia and some
mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin is used with doxycycline and metronidazole to treat pelvic inflammatory disease. Nalidixic acid is an older quinolone effective in uncomplicated urinary-tract infections and, in the treatment of shigella in areas where it remains susceptible.

CIPROFLOXACIN

Ciprofloxacin is a representative quinolone antibacterial. Various drugs can serve as alternatives

**Tablets**, ciprofloxacin (as hydrochloride) 250 mg, 500 mg
Intravenous infusion, ciprofloxacin (as lactate) 400 mg

**Uses**
gastroenteritis—including cholera, shigellosis, travellers’ diarrhoea, campylobacter and salmonella enteritis; typhoid; gonorrhoea; chancroid; legionnaires’ disease; meningitis (including meningococcal meningitis prophylaxis); respiratory-tract infections—including pseudomonal infections in cystic fibrosis, but not pneumococcal pneumonia; urinary-tract infections; bone and joint infections; septicaemia; anthrax; skin infections; prophylaxis in surgery

**Contraindications**
History of tendon disorders related to quinolone use

**Precautions**
history of epilepsy or conditions that predispose to seizures, G6PD deficiency, myasthenia gravis (risk of exacerbation), pregnancy (Appendix 2), breastfeeding (Appendix 3), children or adolescents (see below); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely, tendon damage—discontinue at first sign of pain or inflammation and rest affected limb; hepatic impairment (Appendix 5); renal failure (Appendix 4); avoid excessive alkalinity of urine and ensure adequate fluid intake as risk of crystalluria; **interactions:** Appendix 1

**USE IN CHILDREN.** Ciprofloxacin causes arthropathy in the weight-bearing joints of immature animals and is therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of ciprofloxacin in children may be justified. Ciprofloxacin is used for pseudomonal infections in cystic fibrosis (for children over 5 years), and for treatment and prophylaxis of anthrax

**Patient Advice.**
May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage**
Infections due to susceptible organisms, by mouth, ADULT 250–750 mg twice daily

Acute uncomplicated cystitis, by mouth, ADULT 100 mg twice daily for 3 days
Gonorrhoea, chancroid, shigellosis, or cholera, by mouth, 500 mg as a single dose
Pseudomonal lower respiratory-tract infection in cystic fibrosis, by mouth, ADULT 750 mg twice daily; CHILD 5–17 years (see Precautions) up to 20 mg/kg twice daily (maximum 1.5 g daily)
Surgical prophylaxis, by mouth, ADULT 750 mg 60–90 minutes before procedure
Prophylaxis of meningococcal meningitis, by mouth, ADULT 500 mg as a single dose

Adverse effects
nausea, vomiting, dyspepsia, abdominal pain, flatulence, diarrhoea (rarely antibiotic-associated colitis), dysphagia, tremor, hyperglycaemia, headache, dizziness, sleep disorders, rash (rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis), and pruritus; vasculitis, erythema nodosum, petechiae, haemorrhagic bullae; less frequently anorexia, increase in blood urea and creatinine; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia, and anaphylaxis; blood disorders (including eosinophilia, leukopenia, thrombocytopenia), altered prothrombin time; disturbances in vision, taste, hearing and smell, tinnitus; tenosynovitis; tachycardia, oedema, syncope, hot flushes and sweating; also isolated reports of tendon inflammation and damage (especially in the elderly and in those taking corticosteroids), haemolytic anaemia, renal failure, interstitial nephritis, and hepatic dysfunction (including hepatitis and cholestatic jaundice); if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur discontinue

Tetracyclines

**Doxycycline** is a tetracycline and is a broad-spectrum antibiotic effective for conditions caused by chlamydia, rickettsia, brucella and the spirochaete, *Borrelia burgdorferi* (Lyme disease). It is the preferred tetracycline since it has a more favourable pharmacokinetic profile than tetracycline. It is deposited in growing bone and teeth causing staining and occasionally dental hypoplasia. It should not be given to children under 8 years or pregnant women; in some countries, use in children under 12 years is contraindicated.

**DOXYCYCLINE**

Capsules, doxycycline (as hydrochloride) 100 mg

Uses
Respiratory-tract infections, including pneumonia and chronic bronchitis; urinary-tract infections; syphilis; chlamydia, mycoplasma, and rickettsia; prostatitis; lymphogranuloma venereum; pelvic inflammatory disease (with metronidazole); Lyme disease; brucellosis (with rifampicin); leptospirosis, scrub typhus and travellers’ diarrhoea; psittacosis; cholera; melioidosis; plague; anthrax; Q fever; malaria (section 6.4.3)

Contraindications
Pregnancy (Appendix 2); children (see notes above); porphyria; systemic lupus erythematosus

Precautions
Avoid exposure to sunlight or sunlamps—photosensitivity reported; renal impairment (Appendix 4); hepatic impairment (Appendix 5); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage
Infections due to susceptible organisms, by mouth, ADULT and CHILD over 8 years, 200 mg on first day then 100 mg daily; in severe infections, 200 mg daily
Syphilis, by mouth, 100 mg twice daily for 14 days; late latent syphilis 100 mg twice daily for 28 days
Uncomplicated genital chlamydia, non-gonococcal urethritis, by mouth, 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease)
Louse and tick-borne relapsing fevers, by mouth, 100 mg or 200 mg as a single dose
Cholera, by mouth, ADULT 300 mg as a single dose; CHILD over 8 years, 100 mg as a single dose

Patient Advice.
Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. May be given with milk or food to counter gastric irritation

Adverse effects:
Gastrointestinal disturbances; anorexia, erythema (discontinue treatment); photosensitivity; hypersensitivity reactions; headache and visual disturbances; hepatotoxicity, blood disorders, pancreatitis, and antibiotic-associated colitis reported; staining of growing teeth and occasional dental hypoplasia

Macrolides
Erythromycin is a macrolide; it has an antibacterial spectrum that is similar but not identical to penicillin and is used as an alternative in penicillin-allergic patients. It is effective in respiratory infections, whooping cough, Legionnaires’ disease and campylobacter enteritis.
Azithromycin is more active than erythromycin against some Gram-negative organisms such as *Chlamydia trachomatis*. The
concentration and persistence of azithromycin is much higher in the tissue than in plasma; a single dose of azithromycin is used in the treatment of uncomplicated genital chlamydia and trachoma. Azithromycin is not recommended if there is a possibility of gonorrhoea because macrolide resistance emerges rapidly when it is used in this setting.

**Azithromycin (SAD)**

*Capsules*, azithromycin (as dihydrate) 250 mg or 500 mg  
*Oral suspension*, azithromycin (as dihydrate) 200 mg/5 ml

**Uses**  
Uncomplicated genital chlamydial infections and trachoma

**Contraindications**  
Hepatic impairment (Appendix 5)

**Precautions**  
Renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); prolongation of QT interval (ventricular tachycardia reported); **interactions**: Appendix 1

**Dosage**  
Uncomplicated genital chlamydial infections or trachoma, by mouth, **ADULT** over 45 kg 1 g as a single dose; under 45 kg 20 mg/kg as a single dose

**PATIENT ADVICE.**

Not to be taken at the same time as aluminium- or magnesium-containing indigestion remedies. Capsules should be taken at least 1 hour before or 2 hours after food; oral suspension can be taken with food

**Adverse effects**

see under Erythromycin (but fewer gastrointestinal effects); also anorexia, dyspepsia, constipation; dizziness, headache, drowsiness; photosensitivity; hepatitis, interstitial nephritis, acute renal failure, asthenia, paraesthesia, convulsions and mild neutropenia reported; rarely tinnitus, hepatic necrosis, hepatic failure, and taste disturbances

**ERYTHROMYCIN**

Erythromycin is a representative macrolide antibiotic. Various drugs can serve as alternatives  
*Tablets*, erythromycin (as stearate) 250 mg; erythromycin (as ethyl succinate) 500 mg  
*Oral suspension*, erythromycin (as stearate) 125 mg/5 ml; erythromycin (as ethyl succinate) 125 mg/5 ml

**Uses**

alternative to penicillin in hypersensitive patients; pneumonia;  
legionnaires’ disease; syphilis; chancroid; chlamydia; non-gonococcal urethritis; prostatitis; lymphogranuloma venereum; campylobacter enteritis; relapsing fever; diphtheria and whoop-
ing cough prophylaxis

**Contraindications**
Hypersensitivity to erythromycin or other macrolides; porphyria

**Precautions**
Hepatic impairment (Appendix 5) and renal impairment (Appendix 4); prolongation of the QT interval (ventricular tachycardia reported); pregnancy (not known to be harmful); breastfeeding (Appendix 3); **interactions:** Appendix 1

**Dosage**
Infections due to sensitive organisms, *by mouth*, ADULT and **CHILD** over 8 years, 250–500 mg every 6 hours; up to 4 g daily in severe infections; **CHILD** up to 2 years, 125 mg every 6 hours, doubled in severe infections; **CHILD** 2–8 years, 250 mg every 6 hours, doubled in severe infections

Early syphilis, *by mouth*, **ADULT** 500 mg 4 times daily for 14 days

Uncomplicated genital chlamydia, non-gonococcal urethritis, *by mouth*, **ADULT** 500 mg 4 times daily for 7 days

Severe infections, *by intravenous infusion*, **ADULT** and **CHILD** 50 mg/kg daily by continuous infusion or in divided doses every 6 hours

**Patient Advice.**
Gastro-resistant tablets and capsules should be swallowed whole

**Adverse effects:**
nausea, vomiting, abdominal discomfort, diarrhoea (and antibiotic-associated colitis); urticaria, rashes, and other allergic reactions (rarely, anaphylaxis); reversible hearing loss after large doses; cholestatic jaundice, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis

**AMINOGLYCOSIDES**
Aminoglycosides including gentamicin and amikacin are bactericidal and active against some Gram-positive and many Gram-negative organisms including *Pseudomonas aeruginosa*. Aminoglycosides are not absorbed from the gut and must therefore be given by injection for systemic infections. Excretion is mainly by the kidney and accumulation occurs in renal impairment.

Use of gentamicin should be restricted to trained health personnel and care must be taken to ensure correct dosage and duration of treatment are not exceeded, because most adverse effects are dose related. The most important adverse effects are ototoxicity and nephrotoxicity and they are most common in the elderly and in patients with renal impairment. These groups
and, if possible, all patients should be monitored for ototoxicity by audiometry. If there is impairment of renal function the dose interval must be increased; in severe renal impairment, the dose should also be reduced. Serum concentration monitoring avoids both excessive and subtherapeutic concentrations and can prevent toxicity and ensure efficacy. If possible serum concentrations should be monitored in all patients, but must be measured in infants, the elderly, in obesity, in cystic fibrosis, in high-dosage regimens, in renal impairment, or if treatment lasts for longer than 7 days.

For most infections, doses of up to 5 mg/kg daily in divided doses are used if renal function is normal; higher doses are used occasionally for serious infections. Loading and maintenance doses are based on the patient’s weight and renal function (for example, using a nomogram) with adjustments based on plasma gentamicin concentration.

**GENTAMICIN**

Gentamicin is a representative aminoglycoside antibiotic. Various drugs can serve as alternatives.

*Injection (Solution for injection), gentamicin (as sulfate) 10 mg/ml, 2-ml vial; 40 mg/ml, 2-ml vial*

**Uses**

pneumonia; cholecystitis; peritonitis; septicemia; acute pyelonephritis; prostatitis; skin infections; pelvic inflammatory disease; endocarditis; meningitis; listeriosis; tularaemia; brucellosis; plague; surgical prophylaxis; eye (section 21.1)

**Contraindications**

Myasthenia gravis

**Precautions**

Renal impairment (Appendix 4), infants and elderly (dosage adjustment and monitor renal, auditory, and vestibular function, and serum-gentamicin concentrations); avoid prolonged use; conditions characterized by muscular weakness; significant obesity (monitor serum-gentamicin concentration closely and possibly reduce dose); see notes above; pregnancy (Appendix 2); interactions: Appendix 1

**Dosage**

Infections due to susceptible organisms, by intramuscular injection or by slow intravenous injection (over at least 3 minutes) or by intravenous infusion, ADULT 3–5 mg/kg daily in divided doses every 8 hours; CHILD up to 2 weeks, 3 mg/kg every 12 hours; 2 weeks–12 years, 2 mg/kg every 8 hours Streptococcal and enterococcal endocarditis (as part of combination therapy), by intravenous injection (over at least 3 minutes), ADULT 80 mg twice daily

Surgical prophylaxis, by intravenous injection, ADULT 5 mg/kg as a single dose at induction (with clindamycin)

**NOTE.**
One hour (peak) concentrations should not exceed 5–10 mg/litre; pre-dose (trough) concentration should be less than 2 mg/litre

**DILUTION AND ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects**
Vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesemia on prolonged therapy; antibiotic-associated colitis; also, nausea, vomiting, rash

**Amikacin**
Amikacin is a derivative of kanamycin and has one important advantage over gentamicin in that it is more stable than gentamicin to enzyme inactivation

**Injection:** amikacin (as sulphate) 250 mg/ml, 2 ml-vial

**Uses:**
Serious Gram-negative infections resistant to gentamicin

**Contraindications:**
See under gentamicin

**Precautions:**
See under gentamicin

**Dosage:**
By intramuscular or slow intravenous injection or by infusion, 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses in severe infections; max. 1.5 g daily for up to 10 days (max.cumulative dose 15g); CHILD 15 mg/kg in two divided doses; NEONATE loading dose of 10 mg/kg then 15 mg/kg daily in 2 divided doses

**Adverse effect:**
See under gentamicin

**Metronidazole**
Metronidazole has high activity against anaerobic bacteria and protozoa (see also section 6.4.1). Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible.

**METRONIDAZOLE**
Metronidazole is a representative antibacterial and antiprotozoal drug. Various drugs can serve as alternatives

- **Tablets**, metronidazole 250 mg
- **Oral suspension**, metronidazole (as benzoate) 200 mg/5 ml
- **Intravenous infusion** (Solution for infusion), metronidazole 5 mg/ml, 100-ml bag
- **Suppository**, metronidazole 0.5 g,

**Uses**
an aerobic bacterial infections, including gingivitis, pelvic inflammatory disease, tetanus, peritonitis, brain abscess, necrotizing pneumonia, antibiotic-associated colitis, leg ulcers and pres-
sure sores and surgical prophylaxis; bacterial vaginosis; tissue nematode infections (section 6.1.1.3); trichomonal vaginitis, amoebiasis, and giardiasis (section 6.4.1); *Helicobacter pylori* eradication (section 17.1)

**Contraindications**
Chronic alcohol dependence

**Precautions**
Disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); clinical and laboratory monitoring in courses lasting longer than 10 days; interactions: Appendix 1

**Dosage**
Anaerobic infections (usually treated for 7 days), by mouth, **ADULT** 800 mg initially then 400 mg every 8 hours or 500 mg every 8 hours; **CHILD** 7.5 mg/kg every 8 hours

Anaerobic infections, by intravenous infusion over 20 minutes, **ADULT** 500 mg every 8 hours; **CHILD** 7.5 mg/kg every 8 hours

Anaerobic infections, by rectum, **ADULT** and **CHILD** over 10 years 1 g every 8 hours for 3 days, then 1 g every 12 hours; **CHILD** up to 1 year, 125 mg every 8 hours for 3 days, then every 12 hours; 1–5 years 250 mg; 5–10 years 500 mg

Bacterial vaginosis, by mouth, **ADULT** 2 g as a single dose or 400–500 mg twice daily for 5–7 days

Pelvic inflammatory disease, by mouth, **ADULT** 400 mg twice daily for 14 days

Leg ulcers and pressure sores, by mouth, **ADULT** 400 mg every 8 hours for 7 days

Acute ulcerative gingivitis, by mouth, 200–250 mg every 8 hours for 3 days; **CHILD** 1–3 years, 50 mg every 8 hours for 3 days; 3–7 years, 100 mg every 12 hours for 3 days; 7–10 years, 100 mg every 8 hours for 3 days

Acute dental infections, by mouth, **ADULT** 200 mg every 8 hours for 3–7 days

Antibiotic-associated colitis, by mouth, 800 mg initially then 400 mg 3 times daily for 10 days

Surgical prophylaxis, by mouth, **ADULT** 400–500 mg 2 hours before surgery; up to 3 further doses of 400–500 mg may be given every 8 hours for high-risk procedures; child 7.5 mg/kg 2 hours before surgery; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

Surgical prophylaxis, by rectum, **ADULT** 1 g 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures; **CHILD** 5–10 years 500 mg 2 hours before surgery; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures

Surgical prophylaxis by intravenous infusion (if rectal administration inappropriate), **ADULT** 500 mg at induction; up to 3
further doses of 500 mg may be given every 8 hours for high-risk procedures; **CHILD** 7.5 mg/kg at induction; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

**Patient Advice.**

Metronidazole tablets should be swallowed whole with water, during or after a meal; metronidazole suspension should be taken one hour before a meal

**Adverse effects:**

nausea, vomiting, unpleasant metallic taste, furred tongue and gastrointestinal disturbances; rarely, headache, drowsiness, dizziness, ataxia, darkening of urine, erythema multiforme, pruritus, urticaria, angioedema, and anaphylaxis; abnormal liver function tests, hepatitis, jaundice, thrombocytopenia, aplastic anaemia, myalgia, arthralgia; peripheral neuropathy, epileptiform seizures, leukopenia, on prolonged or high dosage regimens

**Nitrofurantoin**

**Nitrofurantoin** is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens and it is used to treat acute and recurrent urinary-tract infections. It is also used prophylactically in chronic urinary-tract infections.

**NITROFURANTOIN**

*Tablets*, nitrofurantoin 100 mg

**Uses**

Urinary-tract infections

**Contraindications**

Impaired renal function (Appendix 4); infants less than 3 months; G6PD-deficiency including breastfeeding of affected infants (Appendix 3); pregnancy, at term (Appendix 2); porphyria

**Precautions**

Pulmonary disorders or hepatic impairment (Appendix 5); monitor lung and liver function on long-term therapy (discontinue if lung function deteriorates); neurological or allergic disorders; anaemia; diabetes mellitus; elderly and debilitated; vitamin B and folate deficiency; false positive urinary glucose (if testing for reducing substances); urine may be coloured yellow or brown

**Dosage**

Acute uncomplicated urinary-tract infections, *by mouth*, **ADULT** 100 mg every 12 hours or 50 mg every 6 hours with food for 7 days; **CHILD** over 3 months, 3 mg/kg daily in 4 divided doses

Severe recurrent urinary-tract infection, by mouth, ADULT 100 mg every 6 hours with food for 7 days (dose reduced to 200 mg daily in divided doses, if severe nausea)
Prophylaxis of urinary-tract infections (see Precautions), by mouth, ADULT 50–100 mg at night; CHILD over 3 months, 1 mg/kg at night

Adverse effects
dose-related gastrointestinal disorders; nausea; hypersensitivity reactions including urticaria, rash, sialadenitis, pruritus, angioedema; anaphylaxis reported; rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis; erythema multiforme, pancreatitis, arthralgia; blood disorders; pulmonary reactions (pulmonary fibrosis; possible association with lupus erythematosus-like syndrome); peripheral neuropathy; benign intracranial hypertension; transient alopecia

Spectinomycin

Spectinomycin is active against Gram-negative organisms including Neisseria gonorrhoea. It is not suitable for the treatment of syphilis and patients being treated for gonorrhoea should be observed for evidence of syphilis. It should be used only when alternative therapies are inappropriate.

SPECTINOMYCIN

Injection (Powder for solution for injection), spectinomycin (as hydrochloride), 2-g vial

Uses
Uncomplicated and disseminated gonorrhoea (see notes above); adult and neonatal gonococcal conjunctivitis; chancre

Precaution
Renal impairment; pregnancy and breastfeeding

Dosage
Uncomplicated gonococcal infections and chancre, by deep intramuscular injection, ADULT 2 g as a single dose (may be increased to 4 g as a single dose divided between 2 injection sites in difficult to treat cases and where there is known antibiotic resistance)
Disseminated gonococcal infections, by deep intramuscular injection, ADULT 2 g twice daily for 7 days
Neonatal gonococcal conjunctivitis, by deep intramuscular injection, neonate 25 mg/kg (maximum 75 mg) as a single dose

RECONSTITUTION AND ADMINISTRATION.
According to manufacturer’s directions

Adverse effects
Nausea, dizziness, fever, urticaria; rarely, anaphylaxis; pain at injection site
Sulfonamides and trimethoprim
The usefulness of sulfonamides is limited by an increasing incidence of bacterial resistance. For many indications they have been replaced by antibiotics that are more active and safer. Sulfadiazine is used in the prevention of rheumatic fever recurrence. Sulfamethoxazole is used in combination with trimethoprim because of their synergistic activity. In some countries, indications for the use of this combination have been restricted. The treatment of *Pneumocystis carinii* infections must only be undertaken with specialist supervision where there are appropriate monitoring facilities (section 6.4.5). Trimethoprim is also used alone for respiratory-tract infections and, in particular, for urinary-tract infections.

**Sulfamethoxazole with trimethoprim**

*Tablets*, sulfamethoxazole 400 mg with trimethoprim 80 mg; sulfamethoxazole 800 mg with trimethoprim 160 mg
*Oral suspension*, sulfamethoxazole 200 mg with trimethoprim 40 mg/5 ml
*Injection* (Solution for dilution for infusion), sulfamethoxazole 80 mg with trimethoprim 16 mg/ml, 5-ml and 10-ml ampoules

**Uses**
urinary-tract infections; respiratory-tract infections including bronchitis, pneumonia, infections in cystic fibrosis; melioidosis; listeriosis; brucellosis; granuloma inguinale; otitis media; skin infections; *Pneumocystis carinii* pneumonia (section 6.4.5)

**Contraindications**
Hypersensitivity to sulfonamides or trimethoprim; porphyria

**Precautions**
renal impairment (avoid if severe; Appendix 4); hepatic impairment (avoid if severe; Appendix 5); maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rash—discontinue immediately; predisposition to folate deficiency, elderly; asthma; G6PD deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid in infants under 6 weeks; interactions: Appendix 1

**Dosage**
Severe infections due to susceptible organisms (not susceptible to other antibacterials), *by mouth or by intravenous infusion*,
*ADULT* sulfamethoxazole 800 mg with trimethoprim 160 mg every 12 hours, increased to sulfamethoxazole 1.2 g with trimethoprim 240 mg, every 12 hours in more severe infections; *by mouth*, *CHILD* 6 weeks–5 months, sulfamethoxazole 100 mg with trimethoprim 20 mg every 12 hours; 6 months–5
years, sulfamethoxazole 200 mg with trimethoprim 40 mg every 12 hours; 6–12 years, sulfamethoxazole 400 mg with trimethoprim 80 mg every 12 hours; by intravenous infusion, CHILD sulfamethoxazole 30 mg/kg daily with trimethoprim 6 mg/kg daily in 2 divided doses

**DILUTION AND ADMINISTRATION.**

According to manufacturer’s directions

**Adverse effects**

nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum; rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; systemic lupus erythematosus, myocarditis, serum sickness; crystalluria—resulting in haematuria, oliguria, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, ataxia, tinnitus, vertigo, dizziness, hallucinations, and electrolyte disturbances; megaloblastic anaemia due to trimethoprim

### 6.4 Antileprosy drugs

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 to 10 years, but may be up to 20 years. It is transmitted from person-to-person when bacilli are shed from the nose; most individuals have natural immunity and symptoms are suppressed. For treatment purposes patients may be classified as having paucibacillary (PB) or multibacillary (MB) leprosy. The 2 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 and choose a regimen based on number of skin lesions; these are PB leprosy (1–5 skin lesions) and MB leprosy (more than 5 skin lesions).

Medicines used in the treatment of leprosy should always be used in combination; this is essential to prevent the emergence of resistance. Rifampicin is now combined with dapsone to treat PB leprosy and rifampicin and clofazimine are now combined with dapsone to treat MB leprosy. The WHO Programme for the Elimination of Leprosy currently provides, free of charge, oral multidrug therapy in colour-coded blister packs (MDT blister packs) to improve patients’ adherence to treatment. Any patient with a positive skin smear should be treated with the MDT regimen for MB leprosy. The regimen for
PB leprosy should never be given to a patient with MB leprosy. If diagnosis classification in a particular patient is not possible the MDT regimen for MB leprosy must be used.

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 during a lepra reaction without interruption. This reduces the frequency and severity of lepra reactions.

Type 1 lepra reactions, or reversal reactions, are delayed hypersensitivity reactions and may occur in either PB or MB leprosy. If there is no nerve damage, type 1 reaction may be treated with analgesics such as acetylsalicylic acid or paracetamol. If there is nerve involvement corticosteroids, such as oral prednisolone should be used in addition to analgesics.

The type 2 lepra reaction, also known as erythema nodosum leprosum (ENL), is an antibody response to dead leprosy bacteria and occurs only in MB leprosy. Therapy for type 2 reactions may include analgesics, such as acetylsalicylic acid or paracetamol, and a corticosteroid, such as oral prednisolone. In patients not responding to a corticosteroid, clofazimine may be used. Severe type 2 lepra reactions should be treated under medical supervision in hospital.

If a patient does not respond to lepra reaction treatment within 6 weeks or seems to become worse, the patient must be sent immediately to the nearest specialist centre. Neuritis may occur during or independently of lepra reactions. It can be successfully treated with a 12-week course of oral prednisolone; if patients do not respond, specialist centre treatment is required.

**TREATMENT REGIMENS**

The recommended regimen for paucibacillary leprosy in adults (50–70 kg) is rifampicin 600 mg once monthly and dapsone 100 mg daily. Children aged 10–14 years may be given rifampicin 450 mg once monthly and dapsone 50 mg daily. Appropriate dosage adjustments are required for younger children. For example, dapsone 25 mg daily and rifampicin 300 mg once a month. Treatment is continued for 6 months for PB leprosy.

The recommended regimen for multibacillary (MB) leprosy in adults (50–70 kg) is rifampicin 600 mg and clofazimine 300 mg, both given once a month together with clofazimine 50 mg and dapsone 100 mg, both daily. Children aged 10–14 years may be given rifampicin 450 mg and clofazimine 150 mg, both once a month together with clofazimine 50 mg every other day and dapsone 50 mg daily. Appropriate dosage adjustments are required for younger children. For example, dapsone 25 mg daily, clofazimine 50 mg twice a week, and clofazimine 100 mg and rifampicin 300 mg once a month. Treatment is continued for 12 months for MB leprosy.

For patients who cannot take rifampicin because of allergy,
other diseases, or rifampicin-resistant leprosy, and for patients who refuse to take clofazimine, there are alternative regimens which incorporate ofloxacin and minocycline [not included on WHO Model List].

**RIFAMPICIN**

*Tablets.* rifampicin 150 mg, 300 mg  
*Capsules.* rifampicin 150 mg, 300 mg  

**Uses**  
Paucibacillary leprosy; multibacillary leprosy; tuberculosis (section 6.2.4)  

**Contraindications**  
Hypersensitivity to rifamycins; jaundice  

**Precautions**  
reduce dose in hepatic impairment (Appendix 5); liver function tests and blood counts required in liver disorders, alcohol dependency, elderly, and on prolonged therapy; renal impairment (if dose above 600 mg daily); pregnancy (Appendix 2); breastfeeding (Appendix 3); porphyria; discolours soft contact lenses; **important:** advise patients on oral contraceptives to use additional means; **interactions:** Appendix 1  

**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  

**Dosage**  
Paucibacillary leprosy (in combination with dapsone; see notes above), *by mouth,* **ADULT** 600 mg once a month; **CHILD** under 10 years, see notes above; 10–14 years 450 mg once a month; continue treatment for 6 months  
Multibacillary leprosy (in combination with dapsone and clofazimine; see notes above), *by mouth,* **ADULT** 600 mg once a month under supervision; **CHILD** under 10 years, see notes above; 10–14 years 450 mg once a month under supervision; continue treatment for 12 months  

**Patient Advice.**  
Take dose at least 30 minutes before a meal, since absorption is reduced by food  

**Adverse effects**  
Severe gastrointestinal disturbances including anorexia, nausea, vomiting, and diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; rashes, fever, influenza-like
syndrome and respiratory symptoms, collapse, shock, hae-molytic anaemia, acute renal failure, and thrombocytopenic purpura—more frequent with intermittent therapy; alterations of liver function—jaundice and potentially fatal hepatitis (dose-related; do not exceed maximum daily dose of 600 mg); also reported, oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia and menstrual disturbances; urine, tears, saliva, and sputum coloured orange-red

6.5 Antituberculosis drugs

Tuberculosis is a chronic infectious disease caused primarily by Mycobacterium tuberculosis or sometimes M. bovis. Infection is usually due to inhalation of infected droplet nuclei with the lung generally being the first organ affected, but the primary infection is usually asymptomatic. Infection and inflammatory responses resolve with the development of acquired immunity. Surviving bacteria may become dormant or in susceptible patients, progress to active primary disease; dormant organisms may produce disease and this often occurs if immune status is altered.

Tuberculosis is the most prevalent infectious disease of adults and causes 26% of avoidable adult deaths in the developing world. More than 80% of tuberculosis cases are pulmonary (PTB). At least 30% of patients who are infected with HIV will also develop active tuberculosis. The increase in resistant strains and poor compliance which may contribute to resistance and treatment failure has led to the development of regimens with directly supervised treatment. Directly observed treatment, short-course (DOTS) therapy which lasts for 6 or 8 months, given under direct observation is one of the most important components of the WHO strategy against tuberculosis. Simplified drug regimens and intermittent therapy have been introduced to improve compliance. WHO does not generally recommend twice weekly regimens. If a patient receiving a twice weekly regimen misses a dose of tablets, the missed dose represents a bigger fraction of the total number of treatment doses than if the patient was receiving a three times weekly or daily dose regimen. Therefore, there is a greater risk of treatment failure with twice weekly regimens. Fixed-dose combination tablets incorporating 2 or more drugs are also used to improve compliance and decrease medication errors; they should be used unless one of the components cannot be given because of resistance or intolerance.

Modern short-course therapy is usually in 2 phases. The initial phase (2 months) involves the concurrent use of at least 3 drugs
to reduce the bacterial population rapidly and prevent drug-resistant bacteria emerging. The second continuation phase (4–6 months) involves fewer drugs and is used to eliminate any remaining bacteria and prevent recurrence. Direct observation of therapy is considered essential to ensure compliance in the initial phase and also useful in the continuation phase if patients are receiving rifampicin. Five antituberculosis drugs, isoniazid, rifampicin, pyrazinamide, streptomycin, (which are bactericidal) and ethambutol (which is bacteriostatic) are used in various combinations as part of WHO-recommended treatment regimens; thiacetazone is used only if ethambutol cannot be used. In supervised regimens change of drug regimen should be considered only if the patient fails to respond after 5 months of DOTS.

Isoniazid, rifampicin, and pyrazinamide are components of all antituberculosis drug regimens currently recommended by WHO. Unsupervised and alternative regimens as set out in the following tables may be administered as specified.

Additional reserve antituberculosis drugs (amikacin, p-aminosalicylic acid, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, levofoxacin, and ofloxacin) for the treatment of multidrug-resistant tuberculosis should be used in specialized centres adhering to WHO standards for TB control.

Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is human immunodeficiency virus (HIV) infection; it increases susceptibility to primary infection and increases the reactivation rate of tuberculosis. Preventative antituberculosis therapy of such persons is recommended.

Chemoprophylaxis with isoniazid can prevent the development of clinically apparent disease in persons in close contact with infectious patients, and also prevent the reactivation of previously dormant disease in other persons at high risk particularly those who are immunodeficient.

Where the disease remains highly prevalent routine immunization of infants within the first year of age with BCG vaccine is cost-effective. However, there is no evidence that BCG will protect children older than 15 years of age. Infants born to HIV-positive mothers should be vaccinated during the first year of life, provided they have no clinical signs suggestive of HIV.

The tuberculin test has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or
between acquired infection and seroconversion induced by BCG vaccination.
**Recommended 6-month treatment regimens for tuberculosis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial phase (2 months)</th>
<th>Continuation phase (4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg daily</td>
<td>5 mg/kg daily</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg daily</td>
<td>10 mg/kg daily</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td><strong>together with</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td><strong>or</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg daily</td>
<td>10 mg/kg 3x wkly.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>10 mg/kg 3x wkly.</td>
<td>10 mg/kg 3x wkly.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg 3x wkly.</td>
<td>10 mg/kg 3x wkly.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>35 mg/kg 3x wkly.</td>
<td></td>
</tr>
<tr>
<td><strong>together with</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg 3x wkly.</td>
<td></td>
</tr>
<tr>
<td><strong>or</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>30 mg/kg 3x weekly²</td>
<td></td>
</tr>
</tbody>
</table>

1 Unless otherwise indicated, doses are suitable for both adults and children
2 Not suitable for children

### Recommended 8-month treatment regimen for tuberculosis

**Drug**

<table>
<thead>
<tr>
<th>Initial phase (2 months)</th>
<th>Continuation phase (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid 5 mg/kg daily</td>
<td>5 mg/kg daily</td>
</tr>
<tr>
<td>Rifampicin 10 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide 25 mg/kg daily</td>
<td>Ethambutol 15 mg/kg daily³</td>
</tr>
<tr>
<td><strong>together with</strong></td>
<td><strong>or</strong> Streptomycin² 15 mg/kg daily</td>
</tr>
</tbody>
</table>

1 Unless otherwise indicated, doses are suitable for both adults and children
2 Streptomycin always replaces ethambutol in meningeal TB
3 Not suitable for children under 5 years
4 Thioacetazone (2.5 mg/kg daily) may be used (only if ethambutol cannot be given) in combination with isoniazid in the continuation phase; risk of severe toxicity, particularly in HIV-infected individuals

### Treatment regimens by category of tuberculosis diagnosis

**Category I: New pulmonary disease (smear-positive or smear-negative with extensive involvement of parenchyma), concomitant severe HIV disease, and new severe extra-pulmonary disease**

*Initial phase* ¹ (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + pyrazinamide + ethambutol (or streptomycin) for 2 months

*Continuation phase* ¹ (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin for 4 months (or isoniazid + ethambutol for 6 months but less effective than isoniazid + rifampicin)

**Category II: Previously treated smear-positive pulmonary**

disease which has relapsed, or failed 2 to respond, or if treatment was interrupted

Initial phase ¹ (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + pyrazinamide + ethambutol + streptomycin for 2 months

then: isoniazid + rifampicin + pyrazinamide + ethambutol for 1 month

Continuation phase ¹ (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + ethambutol for 5 months

Category III: New smear-negative pulmonary disease (other than in Category I) and less severe extra-pulmonary disease

Initial phase ¹ (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin + pyrazinamide + ethambutol ³ for 2 months

Continuation phase ¹ (antibacterials administered daily or 3 times weekly): isoniazid + rifampicin for 4 months (or isoniazid + ethambutol for 6 months but less effective than isoniazid + rifampicin)

Category IV: Chronic and multi-drug-resistant tuberculosis (MDR-TB) (smear-positive despite supervised retreatment) ⁴ specially designed standardized or individualized regimens recommended

¹ Drug intake should be directly observed in patients who are smear positive during the initial phase, and always when rifampicin is given

² Drug sensitivity testing recommended before prescribing Category II treatment in failure cases; patients with MDR-TB should be prescribed Category IV regimen

³ Omit ethambutol in initial phase if disease is not complicated by cavitary disease or concomitant HIV disease, and in patients infected with fully susceptible bacilli or young children with primary tuberculosis

⁴ Early culture and sensitivity testing recommended for contacts of patients with MDR-TB

ETHAMBUTOL HYDROCHLORIDE

Tablets, ethambutol hydrochloride 400 mg

Uses
Tuberculosis, in combination with other drugs (see notes and

tables above)

**Contraindications**

Optic neuritis; children under 5 years—unable to report symptomatic visual disturbances; severe renal impairment

**Precautions**

Visual disturbances—ocular examination recommended before and during treatment (see note below); reduce dose in renal impairment (Appendix 4) and monitor plasma concentration; elderly; pregnancy (not known to be harmful); breastfeeding (Appendix 3)

**NOTE.**

Patients should report visual disturbances immediately and discontinue treatment; children who are incapable of reporting symptomatic visual changes accurately should be given alternative therapy, as should, if possible, any patient who cannot understand warnings about visual adverse effects

**Dosage**

Tuberculosis (initial phase of combination therapy; see notes and tables above), **by mouth**, ADULT 15 mg/kg daily or 30 mg/kg 3 times a week; CHILD 15 mg/kg daily

**NOTE.**

‘Peak’ concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); ‘trough’ (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre)

**Adverse effects:**

Optic neuritis—reduced visual acuity and red/green colour blindness (early changes usually reversible, prompt withdrawal may prevent blindness); peripheral neuritis—especially in legs; gout; rarely, rash, pruritus, urticaria, thrombocytopenia

**ISONIAZID**

*Tablets*, isoniazid 100 mg, 300 mg

**Uses**

Tuberculosis treatment, in combination with other drugs (see notes and tables above); tuberculosis prophylaxis

**Contraindications**

Drug-induced hepatic disease

**Precautions**

hepatic impairment (monitor hepatic function; Appendix 5); malnutrition, chronic alcohol dependence, chronic renal failure (Appendix 4), diabetes mellitus, and HIV infection—prophylactic pyridoxine 10 mg daily required because risk of peripheral neuritis; epilepsy; slow acetylator status (increased risk of adverse effects); history of psychosis; pregnancy (not known to be harmful); breastfeeding (Appendix 3); porphyria; interactions: Appendix 1

**LIVER DISORDERS.** Patients or their carers should be told how
to recognize signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as nausea, vomiting, malaise or jaundice develop

**Dosage**
Tuberculosis, treatment (combination therapy; see also notes and tables), by mouth, ADULT and CHILD 5 mg/kg (4–6 mg/kg) daily (maximum, 300 mg daily), or 10 mg/kg 3 times weekly

Tuberculosis, treatment in critically ill patients unable to take oral therapy (combination therapy), by intramuscular injection, ADULT 200–300 mg as single daily dose; CHILD 10–20 mg/kg daily

Tuberculosis, prophylaxis, by mouth, ADULT 300 mg daily for at least 6 months; CHILD 5 mg/kg daily for at least 6 months

**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

**Adverse effects**
gastrointestinal disorders including nausea and vomiting, diarrhoea and pain, also constipation, dry mouth; hypersensitivity reactions including fever, rashes, joint pain, erythema multiforme, purpura usually during first weeks of treatment; peripheral neuropathy; blood disorders including agranulocytosis, haemolytic anaemia, aplastic anaemia; optic neuritis, toxic psychoses, and convulsions; hepatitis (especially over age of 35 years and regular users of alcohol)—withdraw treatment; also reported, systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia and gynaecomastia

**PYRAZINAMIDE**

*Tablets,* pyrazinamide 400 mg

**Uses:** tuberculosis, in combination with other drugs (see notes and tables above)

**Contraindications:** severe hepatic impairment; porphyria

**Precautions:** hepatic impairment (monitor hepatic function; Appendix 5); renal impairment; diabetes mellitus (monitor blood glucose—may change suddenly); gout; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

**LIVER DISORDERS.** Patients or their carers should be told how to recognize signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

**Dosage:**
Tuberculosis (initial phase of combination therapy; see notes and tables above), *by mouth*, **ADULT** and **CHILD** 25 mg/kg daily or 35 mg/kg 3 times weekly

**Adverse effects:**
Hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting; arthralgia; gout; sideroblastic anaemia; rash, photosensitivity

**RIFAMPICIN**

*Capsules*, rifampicin 150 mg, 300 mg

**Uses:**
Tuberculosis, in combination with other drugs (see notes and tables above); leprosy (section 6.2.3)

**Contraindications**
Hypersensitivity to rifamycins; jaundice

**Precautions**
Reduce dose in hepatic impairment (Appendix 5); liver function tests and blood counts required in liver disorders, alcohol dependency, elderly, and on prolonged therapy; renal impairment (if dose above 600 mg daily); pregnancy (Appendix 2); breastfeeding (Appendix 3); porphyria; discourses soft contact lenses; **important**: advise patients on oral contraceptives to use additional means; **interactions**: Appendix 1

**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

**Dosage**
Tuberculosis (combination therapy; see notes and tables above), *by mouth*, **ADULT** and **CHILD** 10 mg/kg daily or 3 times weekly (maximum dose, 600 mg daily)

**Patient Advice.**
Take dose at least 30 minutes before a meal, as absorption is reduced when taken with food

**Adverse effects**
Severe gastrointestinal disturbances including anorexia, nausea, vomiting, and diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; rashes, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, and thrombocytopenic purpura—more frequent with intermittent therapy; alterations

of liver function—jaundice and potentially fatal hepatitis (dose related; do not exceed maximum dose of 600 mg daily); edema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia and menstrual disturbances reported; urine, tears, saliva, and sputum coloured orange-red

**STREPTOMYCIN**

*Injection* (Powder for solution for injection), streptomycin (as sulfate) 1-g vial

**Uses**

Tuberculosis, in combination with other drugs (see notes and tables above)

**Contraindications**

Hearing disorders; myasthenia gravis; pregnancy (Appendix 2)

**Precautions**

Children—painful injection, avoid use if possible; renal impairment (Appendix 4), infants, and elderly (dosage adjustment and monitor renal, auditory, and vestibular function, and plasma streptomycin concentrations); **interactions**: Appendix 1

**Dosage**

Tuberculosis (initial phase of combination therapy; see notes and tables above), *by deep intramuscular injection*, **ADULT** and **CHILD** 15 mg/kg daily or 3 times a week (patients over 60 years or those weighing less than 50 kg may not tolerate doses above 500–750 mg daily)

**RECONSTITUTION AND ADMINISTRATION.** According to manufacturer’s directions

**NOTE.**

One hour (peak) concentration should be 15–40 mg/litre; pre-dose (trough) concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or those over 50 years)

**Adverse effects**

vestibular and auditory damage, nephrotoxicity; hypersensitivity reactions—withdraw treatment; paraesthesia of mouth; rarely, hypomagnesaemia on prolonged therapy; antibiotic-associated colitis; also, nausea, vomiting, rash; rarely, haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia; pain and abscess at injection site

6.6 **Antifungal drugs**

Fungal infections can be superficial or systemic. Superficial infections affect only the skin, hair, nails or mucous membranes whereas systemic fungal infections affect the body as a whole.

Systemic fungal infections are sometimes caused by inhalation,
ingestion or inoculation of primary pathogens, and sometimes by opportunistic invasion of commensals in patients with lowered host resistance. They are increasing in prevalence not only because of the pandemic of HIV infection, but also because of the rise in illicit intravenous drug use in many countries, and greater use of broad spectrum antibiotics and invasive medical procedures. In immunodeficient patients systemic fungal infections are often disseminated.

Amphotericin B is a lipophilic polyene antibiotic; it is fungistatic against a broad spectrum of pathogenic fungi, including Candida spp., Aspergillus spp., Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Paracoccidioides brasiliensis, Mucor, Absidia and Phicopes spp.; it is active against algal Prototheca spp. and against the Leishmania protozoa. It is used for the empirical treatment of serious fungal infections and is used in conjunction with flucytosine to treat cryptococcal meningitis and systemic candidosis.

Amphotericin B has to be administered parenterally as there is little or no absorption from the gastrointestinal tract; amphotericin B is liable to cause nephrotoxicity. Duration of therapy varies with 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 of continuous treatment. Intrathecal infusion has been used successfully in patients with meningeal coccidioidomycosis.

Fluconazole, an orally active synthetic imidazole derivative, possesses fungistatic activity against dermatophytes, yeasts and other pathogenic fungi. It is widely used in the treatment of serious gastrointestinal and systemic mycoses as well as in the management of superficial infections. Fluconazole is also used to prevent fungal infections in immunocompromised patients. Ketoconazole is better absorbed by mouth than other imidazoles. It has been associated with fatal hepatotoxicity and prescribers should weigh the potential benefit of ketoconazole treatment against the risk of liver damage and should monitor patients both clinically and biochemically.

Miconazole and clotrimazole are imidazole antifungals that are useful in the treatment of skin infections.

Flucytosine is a synthetic fluorinated pyrimidine with a narrow spectrum of antifungal activity, particularly against Cryptococcus and Candida spp. In susceptible fungi, it is converted to fluorouracil by cytosine deaminase. Flucytosine is myelosuppressive and plasma concentrations above 75 micrograms/ml are associated with myelotoxicity.
Griseofulvin is a fungistatic antibiotic derived from *Penicillium griseofulvum* with selective activity against the dermatophytes causing ringworm, *Microsporum canis*, *Trichophyton rubrum* and *T. verrucosum*. It has no activity against pityriasis versicolor or candida infections. Griseofulvin is deposited selectively in keratin precursor cells of skin, hair and nails where it disrupts the mitotic apparatus of fungal cells thus preventing fungal invasion of newly-formed cells. It is unsuitable for prophylactic use. Close attention should be given to hygiene and to possible reservoirs of reinfection in clothing, footwear and bedding.

**Nystatin**, a polyene antifungal antibiotic derived from *Streptomyces noursei*, is effective against infections caused by a wide range of yeasts and yeast-like fungi. It is poorly absorbed from the gastrointestinal tract and it is not absorbed from the skin or mucous membranes when applied topically. It is used for the prophylaxis and treatment of candidosis.

**AMPHOTERICIN B (SAD)**

Amphotericin B is a complementary antifungal drug  
*Injection (Powder for solution for injection), amphotericin B 50-mg vial*

**Uses**

Life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, mucormycosis, sporotrichosis, and candidosis; leishmaniasis (section 6.4.2)

**Precautions**

Close medical supervision throughout treatment and initial test dose required (see note, below); renal impairment (Appendix 4); hepatic and renal function tests; blood counts and plasma electrolyte monitoring; corticosteroids (avoid, except to control reactions); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid rapid infusion (risk of arrhythmias); **interactions**: Appendix 1

**ANAPHYLAXIS.**

Anaphylaxis occurs rarely with intravenous amphotericin B and a test dose is advisable before the first infusion. The patient should be observed for about 30 minutes after the test dose

**Dosage**

Systemic fungal infections, *by intravenous infusion*, **ADULT** and **CHILD** initial test dose of 1 mg over 20–30 minutes, then 250 micrograms/kg daily, gradually increased up to 1 mg/kg daily or in severe infection, up to 1.5 mg/kg daily or on alternate days
NOTE.
Prolonged treatment usually necessary; if interrupted for longer than 7 days, recommence at 250 micrograms/kg daily and increase gradually

RECONSTITUTION AND ADMINISTRATION. According to manufacturer’s directions

Adverse effects
fever, headache, anorexia, weight loss, nausea and vomiting, malaise, diarrhoea, muscle and joint pain, dyspepsia, and epigastric pain; renal function disturbances including hypokalaemia, hypomagnesaemia and renal toxicity; blood disorders; cardiovascular toxicity (including arrhythmias); neurological disorders (including peripheral neuropathy); abnormal liver function (discontinue treatment); rash; anaphylactoid reactions (see above); pain and thrombophlebitis at injection site

FLUCONAZOLE

Fluconazole is a representativeazole antifungal. Various drugs can serve as alternatives
Capsules, fluconazole 150 mg, 200mg
Oral suspension (Powder for oral suspension), fluconazole 50 mg/5 ml
Infusion (Solution for infusion), fluconazole 2 mg/ml, 25-ml bottle, 100-ml bottle

Uses
Systemic mycoses including histoplasmosis, non-meningeal coccidiodomycosis, paracoccidioidomycosis and blastomycosis; treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; oesophageal and oropharyngeal candidosis, vaginal candidosis and systemic candidosis

Precautions
Renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3); monitor liver function—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis; Appendix 5); interactions: Appendix 1

Dosage
Systemic mycoses, by mouth or by intravenous infusion
ADULT 200 mg daily for at least 6 months; CHILD over 2 years 3–6 mg/kg daily for at least 6 months
Cryptococcal meningitis (following amphotericin B induction therapy), by mouth or by intravenous infusion
ADULT 800 mg daily for 2 days, then 400 mg daily for 8 weeks; CHILD 6–12 mg/kg daily (every 72 hours in neonates up to 2 weeks old, every 48 hours in neonates 2–4 weeks old)
Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, by mouth or by intravenous infusion
ADULT 100–200 mg daily

Fluconazole is a representative azole antifungal. Various drugs can serve as alternatives
Capsules, fluconazole 150 mg, 200mg
Oral suspension (Powder for oral suspension), fluconazole 50 mg/5 ml
Infusion (Solution for infusion), fluconazole 2 mg/ml, 25-ml bottle, 100-ml bottle

Uses
Systemic mycoses including histoplasmosis, non-meningeal coccidiodomycosis, paracoccidioidomycosis and blastomycosis; treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; oesophageal and oropharyngeal candidosis, vaginal candidosis and systemic candidosis

Precautions
Renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3); monitor liver function—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis; Appendix 5); interactions: Appendix 1

Dosage
Systemic mycoses, by mouth or by intravenous infusion
ADULT 200 mg daily for at least 6 months; CHILD over 2 years 3–6 mg/kg daily for at least 6 months
Cryptococcal meningitis (following amphotericin B induction therapy), by mouth or by intravenous infusion
ADULT 800 mg daily for 2 days, then 400 mg daily for 8 weeks; CHILD 6–12 mg/kg daily (every 72 hours in neonates up to 2 weeks old, every 48 hours in neonates 2–4 weeks old)
Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, by mouth or by intravenous infusion
ADULT 100–200 mg daily

Systemic candidosis (in patients unable to tolerate amphotericin B), **by mouth or by intravenous infusion**, ADULT 400 mg as initial dose, then 200 mg daily for at least 4 weeks; CHILD 6–12 mg/kg daily (every 72 hours in neonates up to 2 weeks old, and every 48 hours in neonates 2–4 weeks old)

Oesophageal and oropharyngeal candidosis, **by mouth or by intravenous infusion**, ADULT 200 mg as an initial dose, then 100 mg daily until symptoms resolved; up to 400 mg daily in very resistant infections; CHILD 3–6 mg/kg on the first day, then 3 mg/kg daily (every 72 hours in neonates up to 2 weeks old, every 48 hours in neonates 2–4 weeks old)

Vaginal candidosis, **by mouth**, ADULT 150 mg as a single dose

**Adverse effects**

nausea, vomiting, abdominal pain; flatulence, diarrhoea; headache, taste disturbance, hepatic disorders, dizziness, seizures, alopecia, pruritus; rash (withdraw treatment); angioedema, anaphylaxis, bullous lesions, toxic epidermal necrolysis and erythema multiforme (Stevens-Johnson syndrome) reported (skin reactions more common in AIDS); hyperlipidaemia, leukopenia, thrombocytopenia, hypokalaemia

**KETOCONAZOLE (SAD)**

*Tablet,* ketoconazole 200mg

**Uses**

Systemic mycoses, serious resistant gastrointestinal mycoses, serious chronic mucocutaneous candidiasis, chronic resistant vaginal candidiasis, resistant dermatophyte infections of skin or fingers (not toe nails), prophylaxis of mycoses in immunosuppressed patients

**Precautions**

Monitor liver function clinically and biochemically- for treatment lasting for more than 14 days, perform liver function tests before starting, 14 days after starting, and then at monthly intervals.

**Dosage:**

200 mg once daily with food, usually for 14 days; if response is inadequate after 14 days continue until at least one week after symptoms have cleared and cultures negative; max. 400 mg (elderly 200 mg) daily. Child: 3 mg/kg daily

Chronic resistant vaginal candidiasis, 400mg once daily with food for 5 days

Prophylaxis and maintenance treatment in immunosuppressed patients, 200 mg daily

**Adverse effects:**

Nausea, vomiting, abdominal pain, headache, rashes, urticaria, pruritis, dizziness
MICONAZOLE

Cream, miconazole nitrate 1%

Uses:
Fungal skin infections, oral fungal infections, vaginal candidiasis

Cautions:
Contact with eyes and mucous membranes should be avoided.

Dosage:
Apply twice daily continuing for 10 days after lesions have healed; nail infections, apply 1-2 times daily

Adverse effects:
Occasional local irritation and hypersensitivity reactions include mild burning sensation, erythema, and itching. Treatment should be discontinued if these are severe.

CLOTRIMAZOLE

Cream, clotrimazole 1%,
Vaginal tablet, clotrimazole 500 mg

Uses:
Fungal skin infections; vaginal candidiasis

Cautions:
See under miconazole

Dosage:
Cream, apply 2-3 times daily
Pessary, insert 1 at night

Adverse effects:
See under miconazole

FLUCYTOSINE

Flucytosine is a complementary drug
Capsules, flucytosine 250 mg
Infusion (Solution for infusion), flucytosine 10 mg/ml, 250-ml infusion

Uses:
Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis; adjunct to amphotericin B in systemic candidosis

Precautions:
Elderly; renal impairment (Appendix 4); also use with amphotericin B (both nephrotoxic); liver- and kidney function tests and blood counts required (weekly in renal impairment or in blood disorders); pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Systemic candidosis and cryptococcosis, by intravenous infusion (over 20–40 minutes), ADULT and CHILD 200 mg/kg daily in 4 divided doses, for usually no more than 7 days (at least 4 months in cryptococcal meningitis); extremely sensitive

organisms, 100–150 mg/kg daily in 4 divided doses
Systemic candidosis, initial treatment or after intravenous therapy, *by mouth*, ADULT and CHILD 50–150 mg/kg daily in 4 divided doses

**NOTE.**
For plasma concentration monitoring blood should be taken shortly before starting next infusion (or before next dose by mouth); plasma concentration for optimum response 25–50 mg/litre—should not be allowed to exceed 80 mg/litre

**Adverse effects:**
rash, nausea, vomiting and diarrhoea; alterations in liver function tests; less frequently, confusion, hallucinations, convulsions, headache, sedation, vertigo; blood disorders including leukopenia, potentially fatal thrombocytopenia and aplastic anaemia

**GRISEOFULVIN**

*Tablets,* griseofulvin 500 mg,
*Suspension,* griseofulvin 125 mg/5 ml

**Uses**
fungal infections of the skin, scalp, hair and nails where topical treatment has failed or is inappropriate

**Contraindications**
Severe liver disease (Appendix 5); pregnancy (avoid pregnancy during and for 1 month after treatment; men should not father children within 6 months of treatment; Appendix 2); porphyria; systemic lupus erythematosus and related disorders

**Precautions**
Pre-existing hepatic insufficiency (closely monitor hepatic function throughout treatment); blood disorders (monitor blood count weekly during first month of treatment); breastfeeding;

**interactions:** Appendix 1

**Patient Advice.** May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage**
Superficial fungal infections, *by mouth*, ADULT 0.5–1 g (but not less than 10 mg/kg) daily with food in single or divided doses;

CHILD 10 mg/kg daily with food in single or divided doses

**NOTE.**
Duration of treatment depends on the infection and thickness of keratin at site of infection; at least 4 weeks for skin and hair, at least 6 weeks for scalp ringworm and in severe infection, up to 3 months; 6 months for fingernails and 12 months or more for toenails

**Adverse effects**
headache, nausea, vomiting, diarrhoea, rashes, dizziness, fatigue reported; dry mouth and angular stomatitis; leukopenia, agranulocytosis; proteinuria reported; photosensitivity; lupus
erythematous, toxic epidermal necrolysis, erythema multiforme; serum sickness, angioedema; peripheral neuropathy; confusion and impaired coordination

NYSTATIN

Tablets, nystatin 100 000 units, 500 000 units
Oral suspension, nystatin 100 000 units/ml
Lozenges, nystatin 100 000 units
Pessaries, nystatin 100 000 units

Uses
Oral, oesophageal, intestinal, vaginal, and cutaneous candidosis

Precautions
Pregnancy and breastfeeding (Appendices 2 and 3)

Dosage
Oral candidosis, by mouth, ADULT and CHILD over 1 month, 100 000 units after food 4 times daily
Intestinal and oesophageal candidosis, by mouth, ADULT 500 000 units 4 times daily; CHILD over 1 month 100 000 units 4 times daily; continue for 48 hours after clinical cure
Vaginal candidosis, vaginal administration, ADULT insert 1–2 pessaries at night for at least 2 weeks

Adverse effects
Nausea, vomiting, diarrhoea at high doses; oral irritation and sensitization; rash and rarely, erythema multiforme (Stevens-Johnson syndrome)

6.7 Antiprotozoal drugs

Antiamoebic, antigiardial and antitrichomonal drugs

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, symptomless carriers should be treated with a luminal amoebicide which will reduce the risk of transmission and protect the patient from invasive amoebiasis. Symptomatic (invasive) amoebiasis may be classified as intestinal or extra-intestinal. Intestinal amoebiasis is either amoebic dysentery or non-dysenteric amoebic colitis. Extra-intestinal amoebiasis most commonly involves the liver, but may involve the skin, genito-urinary tract, lung and brain. Invasive amoebiasis is more likely in malnutrition, immunosuppression

and pregnancy. Amoebic dysentery may take a fulminating course in late pregnancy and the puerperium; treatment with **metronidazole** may be life saving. In less severe infection, metronidazole should, if possible, be avoided in the first trimester. All patients with invasive amoebiasis require treatment with a systemically active compound such as **metronidazole**, **ornidazole** and **tinidazole** followed by a luminal amoebicide in order to eliminate any surviving organisms in the colon. Combined preparations are useful.

In severe cases of amoebic dysentery, tetracycline given in combination with a systemic amoebicide lessens the risk of superinfection, intestinal perforation and peritonitis. Hepatic abscesses should be lanced by needle aspiration.

**GIARDIASIS**

Giardiasis is caused by *Giardia intestinalis* and is acquired by oral ingestion of *Giardia* cysts. Giardiasis can be treated with **tinidazole** in a single dose or with another 5-nitroimidazole such as **metronidazole**; both are highly effective and should be offered when practicable to all infected patients. Family and institutional contacts should also be treated. 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.

**TRICHOMONIASIS**

Trichomoniasis is an infection of the genito-urinary tract caused by *Trichomonas vaginalis* and transmission is usually sexual. In women it causes vaginitis although some are asymptomatic. It is usually asymptomatic in men but may cause urethritis. Patients and their sexual partners should be treated with **metronidazole** or other nitroimidazole.

**METRONIDAZOLE**

Metronidazole is a representative antibacterial and antiprotozoal agent. Various drugs can serve as alternatives

**Tablets**, metronidazole 200 mg, 250 mg, 400 mg, 500 mg

**Oral suspension**, metronidazole (as benzoate) 200 mg/5 ml

**Intravenous infusion** (Solution for infusion), metronidazole 5 mg/ml, 100-ml bag

**Uses**

invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections (section 6.1.1.3); bacterial infections (section 6.2.2.6); *Helicobacter pylori* eradication (section 17.1)

**Contraindications**

chronic alcohol dependence

**Precautions**
Disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 5); pregnancy (Appendix 2; see also notes above); breastfeeding (Appendix 3); clinical and laboratory monitoring in courses lasting longer than 10 days; **interactions:** Appendix 1

**Dosage**

Invasive amoebiasis, *by mouth*, ADULT and CHILD 30 mg/kg daily in 3 divided doses for 8–10 days; subsequent course of luminal amoebicide (see notes above)

Invasive amoebiasis (if oral administration not possible), *by intravenous infusion*, ADULT and CHILD 30 mg/kg daily in 3 divided doses (until patient able to complete course with oral drugs); subsequent course of luminal amoebicide (see notes above)

Giardiasis, *by mouth*, ADULT 2 g once daily for 3 days; CHILD 15 mg/kg daily in divided doses for 5–10 days

Urogenital trichomoniasis, *by mouth*, ADULT 2 g as a single dose or 400–500 mg twice daily for 7 days; sexual partners should be treated concomitantly

**NOTE.**
In amoebiasis and giardiasis, various dosage regimens are used and definitive recommendations should be based on local experience

**Patient Advice.**
Metronidazole tablets should be swallowed whole with water, during or after a meal; metronidazole suspension should be taken one hour before a meal

**Adverse effects**

nausea, vomiting, unpleasant metallic taste, furred tongue and gastrointestinal disturbances; rarely headache, drowsiness, dizziness, ataxia, darkening of urine, erythema multiforme, pruritus, urticaria, angioedema, and anaphylaxis; abnormal liver function tests, hepatitis, jaundice, thrombocytopenia, aplastic anaemia, myalgia, arthralgia; peripheral neuropathy, epileptiform seizures, leukopenia, on prolonged or high dosage regimens

**Tinidazole**

Tinidazole is similar to metronidazole but has a longer duration of action.

Tablet, tinidazole 500 mg

**Uses**

see under metronidazole

**Contraindications:**

see under metronidazole

**Precautions:**
see under metronidazole, pregnancy, (manufacturer advises avoid in first trimester)

**Dosage:**

- Anaerobic infections by mouth, 2 g initially, followed by 1 g daily or 500 mg twice daily, usually for 5-6 days.
- Bacterial vaginosis and acute ulcerative gingivitis, a single 2-g dose.
- Abdominal surgery prophylaxis, a single 2-g dose approximately 12 hours before surgery.

**Adverse effects:**

see under metronidazole

**Antileishmanial drugs**

Leishmaniasis is caused by the parasitic protozoa *Leishmania*. It can be categorized as visceral, cutaneous or mucocutaneous. It may be a self-limiting localized skin lesion but may range from this to disseminated progressive disease. In endemic areas there is usually a reservoir of disease in a mammalian host and the usual vectors are sandflies.

**VISCERAL LEISHMANIASIS**

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and *L. infantum* (Old World) and by *L. chagasi* (New World), and it is usually responsive initially to the pentavalent antimony compounds, such as sodium stibogluconate. Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or bone marrow aspirates.

**CUTANEOUS LEISHMANIASIS**

Cutaneous leishmaniasis comprises two conditions. The Old World variety is caused by *L. tropica*, *L. major*, *L. infantum* and *L. aethiopica*. The New World variety is caused by *L. amazonensis*, *L. mexicana*, *L. peruviana*, *L. guyanensis*, *L. panamensis* and *L. braziliensis*. These conditions are characterized by a cell-mediated reaction of varying intensity at the site of inoculation. The New World variety tends to be more severe and slower to heal. Infections caused by *L. major*, *L. mexicana*, *L. tropica* and *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. When the lesion is inflamed or ulcerated or when obstruction of lymphatic drainage or destruction of cartilage creates a risk of serious disfigurement.
or disability, antimonials should be administered systemically as well as locally. Infections due to *L. braziliensis* and the less common *L. panamensis* should be treated with antimonials because of the risk of mucosal involvement. *L. aethiopica* is less responsive at conventional doses and the sores should be left to heal spontaneously if there is no evidence of diffuse cutaneous involvement. *L. guyanensis* infections should be treated with pentamidine.

**MUCOCUTANEOUS LEISHMANIASIS**

Mucocutaneous leishmaniasis is caused by *L. braziliensis* and *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, more extended courses of treatment are often successful. Patients who still fail to respond should receive **amphotericin B** or **pentamidine isetionate**, although neither treatment is highly satisfactory. Because of resistance to antimonials, *L. aethiopica* infections should be treated with pentamidine from the outset until complete healing occurs. 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, and 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 is usually treated with **antimonial compounds**, but relapses must be expected and repeated courses of **pentamidine isetionate** may be needed until clinical immunity is established.

**PENTAVALENT ANTIMONY COMPOUNDS**

Meglumine antimoniate is a representative pentavalent antimony compound used to treat leishmaniasis; sodium stibogluconate can serve as an alternative. *Injection* (Solution for injection), pentavalent antimony (as meglumine antimoniate) 85 mg/ml, 5-ml ampoule; pentavalent antimony (as sodium stibogluconate) 100 mg/ml, 100-ml bottle

**Uses:** leishmaniasis (see notes above)

**Contraindications:**
severe kidney disorders; breastfeeding

Precautions:
provide protein-rich diet throughout treatment and, if possible, correct iron and other nutritional deficiencies; renal and hepatic impairment (Appendices 4 and 5); monitor cardiac, renal and hepatic function—reduce dose or withdraw treatment if abnormalities occur; pregnancy—in potentially fatal visceral leishmaniasis, treat without delay; intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); treat intercurrent infection (for example pneumonia)

MUCOCUTANEOUS DISEASE.
Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroids

Dosage:

NOTE.

Doses are expressed in terms of pentavalent antimony

Visceral leishmaniasis, by intramuscular injection, ADULT and CHILD 20 mg/kg daily for a minimum of 20 days; if relapse, retreat immediately with same daily dosage

Cutaneous leishmaniasis (except L. aethiopica, L. braziliensis, L. amazonensis, by intraläsional injection, ADULT and CHILD 1–3 ml into base of lesion; if no apparent response, may be repeated once or twice at intervals of 1–2 days; by intramuscular injection, ADULT and CHILD 10–20 mg/kg daily until a few days after clinical cure and negative slit-skin smear; relapse is unusual

Cutaneous leishmaniasis (L. braziliensis, by intramuscular injection, ADULT and CHILD 20 mg/kg daily, until lesion has healed and for at least 4 weeks; relapse may occur due to inadequate dosage or interrupted treatment; relapse after full course of treatment requires treatment with pentamidine (see below)

Mucocutaneous leishmaniasis (L. braziliensis, by intramuscular injection, ADULT and CHILD 20 mg/kg daily until slit-skin smears are negative and for at least 4 weeks; if inadequate response, 10–15 mg/kg every 12 hours for same period; if relapse, retreat for at least twice as long; if unresponsive to treatment, treat with pentamidine or amphotericin B (see below)

Diffuse cutaneous leishmaniasis (L. amazonensis, by intramuscular injection, ADULT and CHILD 20 mg/kg daily for several months after clinical improvement occurs; relapse must be expected until immunity develops
ADMINISTRATION.

Meglumine antimoniate may be given by deep intramuscular injection. Sodium stibogluconate may be given by intramuscular injection or by slow intravenous injection (over at least 5 minutes). Both may be administered intralesionally.

Adverse effects:

anorexia, nausea, vomiting, abdominal pain, ECG changes (possibly requiring dose reduction or withdrawal), headache, lethargy, myalgia; raised liver enzymes; renal function impairment; coughing and substernal pain (see Precautions); rarely anaphylaxis, fever, sweating, flushing, vertigo, bleeding from nose or gum, jaundice, rash; pain and thrombosis on intravenous administration; pain on intramuscular injection

Antimalarial drugs

Human malaria, which is transmitted by anopheline mosquitoes (and rarely by congenital transmission, transfusion of infected blood or use of contaminated syringes among drug addicts), is caused by four species of plasmodial parasites. *Plasmodium vivax* is the most extensively distributed and causes much debilitating disease. *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 persist in the liver for many months and even years are responsible for the relapses characteristic of malaria. 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.

Treatment of malaria

This section provides a general overview for the treatment of malaria. However the only products in the formulary for this purpose are chloroquine and pyrimethamine.

Blood schizontocides, which suppress malaria by destroying the asexual blood forms of the parasites, are the mainstay of the treatment of acute malaria and some are used for prophylaxis. They include the 4-aminoquinolines (*amodiaquine* and *chloroquine*), the related arylaminoalcohols (*mefloquine* and *quineine*), and *artemisinin* and its derivatives (*artemether* and *artesunate*). Blood schizontocides are not active against intrahepatic forms and therefore they do not eliminate infections by *P. vivax* and *P. ovale*.

Some antimetabolites act synergistically when given in com-
For example, pyrimethamine in combination with a sulfonamide (sulfadoxine) or sulfone and some antibiotics (for example doxycycline) are blood schizontocides. Because they act more slowly, these substances are of little value when used alone. The tetracyclines are used primarily as adjuncts to quinine where multiple-drug-resistant *P. falciparum* is prevalent.

**Chloroquine**, a rapidly acting schizontocide, is well tolerated, safe and inexpensive. It should be used to treat malaria wherever the parasites remain susceptible. *P. malariae* and *P. ovale* remain fully sensitive to chloroquine. However, chloroquine-resistant strains of *P. falciparum* are widespread in south-east Asia, parts of the Indian subcontinent, South America, Africa and Oceania; strains of *P. vivax* in Papua New Guinea and Indonesia are also resistant to chloroquine.

A 3-day course of chloroquine by mouth is sufficient to eliminate susceptible *P. falciparum* infections because effective plasma-chloroquine concentration is sustained for several weeks. If subsequent relapse occurs in *P. ovale* and *P. vivax* infections primaquine should be administered, after a second course of chloroquine, to eliminate the intrahepatic infection.

**Amodiaquine** is an alternative to chloroquine for the treatment of uncomplicated *P. falciparum* infection; but cross-resistance with chloroquine exists in some areas. It should preferably be used as part of combination therapy with other antimalarials, for example artemesunate. Hepatitis and blood disorders were reported when amodiaquine was used for prophylaxis of malaria; patients should be told how to recognise the symptoms of these conditions and advised to seek medical help if they occur.

The combination of sulfadoxine with pyrimethamine is recommended for the treatment of malaria only in areas of high chloroquine resistance. A single dose of sulfadoxine with pyrimethamine is usually sufficient to eliminate infection; quinine should also be given for 3 days in patients in whom quinine may accelerate reduction of parasitaemia and in those at risk of fulminating disease. However, resistance to these combinations is now widespread, particularly in south-east Asia and South America and it occurs at low prevalence in east and central Africa. Because sulfonamides are associated with a risk of haemolysis and methaemoglobinaemia in the newborn, quinine is preferred to treat chloroquine-resistant malaria during pregnancy (see note on quinine).

**Mefloquine** remains effective except in certain areas of resistance in Thailand, Myanmar and Cambodia. No parenteral preparations are currently available, and it is thus suitable only for patients who can take drugs by mouth. It is generally well tolerated, although, some adverse effects have been reported (see notes). However, because of the danger of the emergence of mefloquine-resistant strains of *P. falciparum* and because of its potential toxicity, it should be used only following either
microscopic or careful clinical diagnosis of *P. falciparum* infections that are known or strongly suspected to be resistant to chloroquine or sulfadoxine with pyrimethamine. **Quinine**, given orally, should be reserved for *P. falciparum* infections likely to be unresponsive to other drugs. Resistance to quinine was, until recently, rare, but the prevalence of resistant strains is now increasing in parts of south-east Asia and South America. Doxycycline, which is an effective oral schizontocide, should be given in combination with quinine except in pregnant women and children under 8 years. In multi-drug resistant malaria, preparations of **artemisinin** or its derivatives (*artemether* or *artesunate*) offer the only prospect of cure. They should not be used in the first trimester of pregnancy. For the treatment of multiresistant falciparum malaria oral *artesunate* may be an effective antimalarial. It should always be given in combination with mefloquine. Parenteral artemether or artemunate, whose use is restricted, are effective alternatives to quinine for the treatment of severe falciparum malaria and are preferred in areas where decreased efficacy of quinine has been documented. To ensure radical cure following parenteral treatment with artemether or oral treatment with artemunate, a full therapeutic dose of mefloquine should be given. A fixed-dose oral formulation of **artemether with lumefantrine** has recently become available and is recommended for the treatment of uncomplicated falciparum malaria in areas with significant resistance. The combination is not for use in pregnancy or breastfeeding.

**Prophylaxis against malaria**

No drug regimen gives assured protection to everybody, and indiscriminate use of antimalarials can increase the risk of inducing resistance. **Chloroquine**, which is usually well tolerated at the required dosage, is preferred where *P. falciparum* remains fully sensitive. The combination of proguanil with chloroquine may overcome mild chloroquine resistance. Chloroquine must be started 1 week before exposure, and be continued in pregnant women until after delivery and for at least 4 weeks after the last risk of exposure in the case of non-immune individuals. This is sufficient to ensure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, whose residual hepatic forms survive. **Mefloquine** may be used for prophylaxis in areas of high risk or where multiple-drug resistance has been reported. Where possible prophylaxis should be started 2–3 weeks before travel to enable any adverse reactions to be identified before exposure (over three-quarters of adverse reactions occur by the third dose) and should be continued for 4 weeks after last
exposure. Mefloquine may be used for prophylaxis during the second and third trimesters. It should be used in early pregnancy only if alternative drugs are either not available or unlikely to be effective and when it is impracticable for the woman to leave the endemic area.

**Proguanil**, a predominantly tissue schizontocide with little blood schizontocidal activity, is a causal prophylactic agent since it is active against pre-erythrocytic intrahepatic forms, particularly of *P. falciparum*. The latent persistent liver forms of *P. ovale* and *P. vivax* are unresponsive. However, there is evidence that it may be effective against *P. vivax* only immediately after the initial infection. *P. falciparum* resistance to proguanil or related compounds may occur in malaria endemic areas and particularly where it has been employed in mass prophylaxis. Proguanil is used for prophylaxis with chloroquine in areas where there is resistance to chloroquine but a low risk of infection as it may give some protection against *P. falciparum* and may alleviate symptoms if an attack occurs. Proguanil and chloroquine may also be used prophylactically in areas of high risk or multi-drug resistance as a second choice where mefloquine is not appropriate.

There is no evidence that proguanil is harmful in prophylactic doses during pregnancy. Because of the vulnerability of pregnant women to *falciparum* malaria, it should be used at full prophylactic dosage wherever the disease is prevalent and likely to be responsive to proguanil, if chloroquine is not available or with chloroquine, if the latter alone is unlikely to be effective.

**CHLOROQUINE**

*Tablets*, chloroquine base (as phosphate or sulfate) 100 mg, 150 mg

*Oral syrup*, chloroquine base (as phosphate or sulfate) 50 mg/5 ml

*Injection* (Solution for injection), chloroquine base (as phosphate or sulfate) 40 mg/ml, 5-ml ampoule

**Uses:**

treatment of acute malaria caused by *P. malariae* and susceptible *P. falciparum*; *P. vivax* and *P. ovale* (followed by primaquine to eliminate intrahepatic forms); prophylaxis of malaria for pregnant women and non-immune individuals at risk; rheumatic disorders (section 2.4)

**Precautions:**

if patient continues to deteriorate after chloroquine—suspect resistance and administer quinine intravenously as emergency measure; hepatic impairment; renal impairment (Appendix 4); pregnancy (but in malaria, benefit considered to outweigh risk; Appendix 2); breastfeeding (Appendix 3); 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; interactions: Appendix 1

Dosage:

NOTE
All doses are in terms of the base

Treatment of malaria, by mouth, ADULT and CHILD 10 mg/kg followed by 5 mg/kg 6–8 hours later; then 5 mg/kg daily on next 2 days (or 10 mg/kg for 2 days, followed by 5 mg/kg daily on day 3); total dose, 25 mg/kg over 3 days

Patient Advice. Oral chloroquine should be taken after meals to minimize nausea and vomiting; if part or all a dose is vomited, the same amount must be immediately readministered

Treatment of malaria (in patients unable to take chloroquine by mouth, but quinine preferred in falciparum malaria), by very slow intravenous infusion (over at least 8 hours), ADULT and CHILD 10 mg/kg as an initial dose, then 2 further infusions of 5 mg/kg at 8-hour intervals (as soon as patient is able to take chloroquine by mouth, discontinue infusions and complete the course with oral preparations total dose, 25 mg/kg over 3 days); by intramuscular or by subcutaneous injection (when intravenous infusion facilities not available) ADULT and CHILD 2.5 mg/kg every 4 hours or 3.5 mg/kg every 6 hours (until total dose of 25 mg/kg administered)

Prophylaxis of malaria, by mouth, ADULT 300 mg once a week; CHILD 5 mg/kg once a week

Patient Advice.
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

Dilution and Administration.
According to manufacturer’s directions. Avoid rapid parenteral administration (risk of toxic plasma concentrations and fatal cardiovascular collapse)

Adverse effects:
headache, gastrointestinal disturbances; also convulsions; visual disturbances (retinopathy associated with long-term, high dose therapy or inappropriate self-medication); depigmentation or loss of hair; rashes; pruritus—may become intolerable; 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

DOXYCYCLINE

Doxycycline is a complementary drug for the treatment of malaria
Capsules, doxycycline (as hydrochloride) 100 mg
Dispersible tablets, doxycycline (as monohydrate) 100 mg

Uses:
supplement to quinine in treatment of multiple-drug resistant P. falciparum malaria (where quinine resistance, in cases of hypersensitivity to sulfonamides); short-term prophylaxis of multiple-drug resistant P. falciparum malaria; bacterial infections (section 6.2.2.3)

Contraindications:
pregnancy (Appendix 2); children under 8 years; porphyria; systemic lupus erythematosus

Precautions:
avoid exposure to sunlight or sunlamps—photosensitivity reported; renal impairment (Appendix 4); hepatic impairment (Appendix 5); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Supplement to malaria treatment (see notes above), by mouth, ADULT and CHILD over 8 years, 100 mg twice daily for 7–10 days
Short-term prophylaxis of malaria, by mouth, ADULT 100 mg daily for up to 8 weeks; CHILD over 8 years, 1.5 mg/kg 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

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

Adverse effects:
gastrointestinal disturbances; anorexia; erythema (discontinue treatment); photosensitivity; hypersensitivity reactions; headache and visual disturbances; hepatotoxicity, blood disorders, pancreatitis and antibiotic-associated colitis reported; staining of growing teeth and occasional dental hypoplasia

PRIMAQUINE
Tablets, primaquine (as phosphate) 7.5 mg, 15 mg

Uses:
elimination of intrahepatic forms of P. vivax and P. ovale (after standard chloroquine therapy); elimination of gametocytes of P. falciparum (after routine therapy with a blood schizontocide)

Contraindications:
pregnancy (treatment with primaquine should be delayed until after delivery; Appendix 2); breastfeeding (Appendix 3); conditions that predispose to granulocytopenia (including active
rheumatoid arthritis and lupus erythematosus

Precautions:
monitor blood count; if methaemoglobinaemia or haemolysis occurs, withdraw treatment and consult physician; G6PD deficiency (exclude before radical treatment for P. vivax and P. ovale, but not before single dose gametocytocidal treatment)

Dosage:
NOTE.
All doses are in terms of the base
Radical treatment of P. vivax and P. ovale malaria (after standard chloroquine therapy), by mouth, ADULT 250 micrograms/kg daily (or 15 mg daily) for 14 days; CHILD 250 micrograms/kg daily for 14 days; in G6PD deficiency, ADULT 750 micrograms/kg once a week for 8 weeks; CHILD 500–750 micrograms/kg once a week for 8 weeks
Gametocytocidal treatment of P. falciparum (after routine blood schizontocide therapy), by mouth, ADULT and CHILD 500–750 micrograms/kg as a single dose

Adverse effects:
anorexia, nausea and vomiting, abdominal pain; acute haemolytic anaemia (frequently in G6PD deficiency); rarely, methaemoglobinaemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia

Antiviral drugs

Herpes and cytomegalovirus infections

HERPES SIMPLEX VIRUS (HSV)

Aciclovir is active against herpes viruses but does not eradicate them. It is only effective if started at onset of infection; it is also used for prevention of recurrence in the immunocompromised. Genital lesions, oesophagitis and proctitis may be treated with oral aciclovir. HSV encephalitis or pneumonitis should be treated with intravenous aciclovir.

Oseltamivir reduces the replication of influenza A and B viruses by inhibiting viral neuraminidase. It is most effective for the treatment of influenza if started within a few hours of the onset symptoms; it is licensed for use within 48 hours of the first symptoms.

HERPES ZOSTER VIRUS

While most HIV positive patients with zoster experience only one self-limiting course, some will experience repeated episodes. Treatment should be reserved for debilitating disease and when there is high risk of serious complications, such as
in advanced HIV disease. Aciclovir is the treatment of choice and it can be administered in high oral dose or in the case of lack of response to oral therapy or CNS involvement, it should be given intravenously.

**Aciclovir**

Aciclovir is a representative drug active against herpes simplex virus and varicella–zoster virus. Various drugs can serve as alternatives

- **Tablets**, aciclovir 400 mg
- **Oral suspension**, aciclovir 200 mg/5 ml
- **Infusion** (Powder for solution for infusion), aciclovir (as sodium salt) 250-mg vial

**Eye ointment, aciclovir 3%**

**Topical cream, aciclovir 5%**

**Uses:**

Treatment of primary genital herpes; disseminated varicella–zoster in immunocompromised patients; herpes simplex encephalitis

**Precautions:**

Maintain adequate hydration; renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3)

**Dosage:**

- Treatment of primary genital herpes, *by mouth*, **ADULT** 200 mg 5 times daily for 7–10 days or 400 mg 3 times daily for 7–10 days
- Prevention of recurrence of genital herpes, *by mouth*, **ADULT** 400 mg twice daily
- Disseminated varicella–zoster in immunocompromised patients, *by intravenous infusion*, **ADULT** 10 mg/kg 3 times daily for 7 days
- Herpes simplex encephalitis, *by intravenous infusion*, **ADULT** 10 mg/kg 3 times daily for 10 days

**RECONSTITUTION AND ADMINISTRATION.**

According to manufacturer’s directions

**Adverse effects:**

Nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; rarely hepatitis, jaundice, dyspnoea, angioedema, anaphylaxis; neurological reactions (including dizziness, confusion, hallucinations, drowsiness), acute renal failure; decreases in haematological indices; on intravenous infusion, severe local inflammation (sometimes resulting in ulceration), fever, agitation, tremor, psychosis, and convulsions

**OSELTMIVIR**

**Capsule**, oseltamivir (as phosphate) 75 mg
Suspension, oseltamivir (as phosphate) for reconstitution with water, 60 mg, 5ml-75ml

**Uses:**
Treatment of uncomplicated, acute influenza A and B infection

**Precautions:**
Renal impairment, pregnancy, breast-feeding

**Dose:**
Prevention of influenza, 75 mg daily for at least 7 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic; CHILD under 12 years safety and efficacy not established.
Treatment of influenza, 75 mg every 12 hours for 5 days; CHILD over 1 year, body-weight 15 kg or under, 30 mg every 12 hours, body-weight 16-23 kg, 45 mg every 12 hours, body-weight 24-40 kg, 60 mg every 12 hours, body-weight over 40 kg, adult dose

**Adverse effects:**
Nausea, vomiting, abdominal pain, dyspepsia, diarrhea, headache, fatigue, insomnia, dizziness, conjunctivitis, epistaxis; ear disorder

**Antiretroviral drugs**

Antiretroviral drugs do not cure HIV (human immunodeficiency virus) infection; they only temporarily suppress viral replication and improve symptoms. Patients receiving these drugs require careful monitoring by appropriately trained health professionals in an adequately resourced setting. Rigorous promotion of measures to prevent new infections remains essential and its need is not diminished by the availability of antiretroviral drugs. Effective therapy requires the simultaneous use of 3 or 4 drugs; alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in cases of intolerance, or to replace failing regimens. The use of a 3- or 4-drug combination as specified in the WHO treatment guidelines is recommended. The use of fixed-dose preparations for these combinations is also recommended if the pharmaceutical quality is assured and interchangeability with the single products is demonstrated as specified by the relevant drug regulatory authority.

Selection of 2 or 3 protease inhibitors from the Model List will need to be determined by each country after consideration of local treatment guidelines and experience, as well as comparative costs of available products. Low-dose ritonavir is used in combination with indinavir, lopinavir or saquinavir as a ‘booster’; ritonavir is not recommended as a drug in its own right.
PRINCIPLES OF TREATMENT
Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible; it should be started before the immune system is irreversibly damaged. The need for early drug treatment should, however, be balanced against the development of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and the patient’s tolerance of it. The development of resistance is reduced by using a combination of 3 or 4 drugs; such combinations should have additive or synergistic activity while ensuring that their toxicity is not additive. Testing for resistance to antiviral drugs, particularly in therapeutic failure, should be considered. Women of childbearing age receiving antiretroviral therapy must have available effective contraceptive methods to prevent unintended pregnancy. Women who are taking non-nucleoside reverse transcriptase inhibitors or protease inhibitors which can lower blood concentration of hormonal oral contraceptives, should be advised to use additional or alternative contraceptives.

DRUGS USED TO TREAT HIV INFECTION
Zidovudine, a nucleoside reverse transcriptase inhibitor (or ‘nucleoside analogue’), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include abacavir, didanosine, lamivudine, and stavudine. The protease inhibitors include, indinavir, lopinavir, and ritonavir. Ritonavir in low doses is used in combination with indinavir, lopinavir or saquinavir as a booster. The small amount of ritonavir in such combinations has no intrinsic antiviral activity but it increases the antiviral activity of the other protease inhibitors by reducing their metabolism. Indinavir, and ritonavir inhibit the cytochrome P450 enzyme system and therefore have a potential for significant drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects (see below). The non-nucleoside reverse transcriptase inhibitors include efavirenz and nevirapine. They interact with a number of drugs metabolized in the liver; the doses of protease inhibitors may need to be increased when they are given with efavirenz or nevirapine. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz but it is usually milder. Efavirenz treatment has also been associated with an increased plasma cholesterol concentration.

INITIATION OF TREATMENT
The time for initiating antiviral treatment is determined by the clinical stage of the HIV infection as indicated by symptoms, and where available, by the CD4-cell count or total lymphocyte count; the plasma viral load, if available, is also a valuable guide for staging the disease (see Monitoring, below).

Recommended initial treatment with a combination of drugs ('highly active antiretroviral therapy', HAART) includes:
- 2 nucleoside reverse transcriptase inhibitors (section 6.5.2.1)
  plus
- a non-nucleoside reverse transcriptase inhibitor (section 6.5.2.2)
  or
- a third nucleoside reverse transcriptase inhibitor (section 6.5.2.1)
  or
- a protease inhibitor which may be combined with ritonavir as booster (section 6.5.2.3).

MONITORING

In resource-limited settings the basic clinical assessment before initiating antiretroviral therapy includes documentation of past medical history, identification of current and past HIV-related illnesses, identification of co-existing medical conditions that may influence the choice of therapy (for example, pregnancy or tuberculosis) as well as current symptoms and physical signs.

The absolute minimum laboratory tests before initiating antiretroviral therapy are an HIV antibody test (in patients over 18 months of age) and a haemoglobin or haematocrit measurement.

Additional basic testing should include:
- white blood cell count;
- differential cell count (to identify a decline in neutrophils and the possibility of neutropenia);
- total lymphocyte count;
- serum alanine or aspartate aminotransferase concentration to assess the possibility of hepatitis co-infection and to monitor for hepatotoxicity;
- serum creatinine and/or blood urea nitrogen to assess baseline renal function;
- serum glucose;
- pregnancy tests for women.

Desirable supplemental tests include measurement of bilirubin, amylase and serum lipids. CD4-cell determinations are, of course, very desirable and efforts should be made to make these widely available. Viral load testing is currently considered optional because of constraints on resources.

CHANGING THERAPY

Deterioration of the condition (including clinical and virological changes) usually calls for replacement of the failing drugs. Intolerance to adverse effects and drug-induced organ dysfunction usually require change in therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance. If treatment fails, a new second-line regimen will be needed. If toxicity occurs, either a new second-line regimen is indicated or, if the toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with another drug that does not have the same adverse effects.

**PREGNANCY**

Treatment of HIV infection in pregnancy aims to:

- minimize the viral load and disease progression in the mother;
- reduce the risk of toxicity to the fetus (although the teratogenic potential of most antiretroviral drugs is unknown);
- prevent transmission of infection to the neonate.

In pregnant women, it may be desirable to initiate antiretroviral therapy after the first trimester, although for pregnant women who are severely ill, the benefit of early therapy outweighs the potential risk to the fetus. All treatment options require careful assessment by a specialist.

The use of zidovudine, lamivudine and nevirapine, are recommended for women of child-bearing potential or who are pregnant. Efavirenz should be avoided because of its potential teratogenic effect on the fetus in the first trimester. First-line treatment in pregnant women should when possible include zidovudine and lamivudine. Monotherapy with either zidovudine or with nevirapine reduces transmission of infection to the neonate (see also below), but combination antiretroviral therapy maximizes the chance of preventing transmission and represents optimal therapy for the mother. Low-dose ritonavir is required if either indinavir or saquinavir is used in pregnancy because adequate drug concentration is achieved only with ritonavir boosting. Information is lacking on the use of lopinavir with ritonavir in pregnancy.

Lactic acidosis and hepatic steatosis associated with nucleoside reverse transcriptase inhibitors may be more frequent in pregnant women and therefore the combination of stavudine and didanosine should be used in pregnancy only when no alternatives are available. Protease inhibitors have been associated with glucose intolerance and pregnant women should be instructed to recognize symptoms of hyperglycaemia and to seek health care advice if they occur.

Various regimens have been used to specifically prevent the
transmission of HIV from mother to the neonate at term. More information is available in *New Data on the Prevention of Mother-to-Child Transmission of HIV and their Policy Implications: Conclusions and Recommendations* (WHO/RHR/01.28), which reflects an inter-agency consultation held on 11–13 October 2000.

**BREASTFEEDING**

Antiretroviral drugs may be present in breastmilk, and may reduce viral load in breastmilk and reduce the risk of transmission through breastfeeding. However, the concentration of antiretroviral drugs in breastmilk may not be adequate to prevent viral replication and there is therefore the possibility of promoting the development of drug-resistant virus which could be transmitted to the infant.

Women with HIV infection should be counselled about the risks of breastfeeding and, where possible, they should limit or avoid breastfeeding; in particular, breastfeeding should be avoided where replacement feeding is acceptable, affordable, sustainable, and safe. HIV-infected women should be counselled on infant feeding options and they should be supported in their choice.

**POST-EXPOSURE PROPHYLAXIS**

Treatment with antiretroviral drugs may be appropriate following occupational exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed and local ones may also be available.

**LIPODYSTROPHY AND METABOLIC EFFECTS**

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients (for example, decreased fat under the skin, increased abdominal fat, ‘buffalo humps’ and breast enlargement). Protease inhibitors are also associated with metabolic abnormalities such as hyperlipidaemia, insulin resistance, and hyperglycaemia. Clinical examination should include an evaluation of fat distribution; measurement of serum lipids and blood glucose should be considered.

Nucleoside reverse transcriptase inhibitors

In some settings it may not be possible to carry out full monitoring described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also notes above)

**ABACAVIR**

ABC

Oral solution, abacavir (as sulfate) 100 mg/5 ml

Uses:
HIV infection in combination with at least two other antiretroviral drugs

Precautions:
hepatic impairment (see below and Appendix 5); renal impairment (Appendix 4); pregnancy (see notes above and Appendix 2); breastfeeding (see notes above)

HYPERSENSITIVITY REACTIONS.
Life-threatening hypersensitivity reactions reported—characterized by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, lethargy, malaise, headache, myalgia and renal failure; less frequently mouth ulceration, oedema, hypotension, dyspnoea, sore throat, cough, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and anaphylaxis (hypersensitivity reactions presenting as sore throat, influenza-like illness, cough and breathlessness identified); rarely 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 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

Patient Advice.
Patients 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 re-starting treatment

HEPATIC DISEASE.
Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported—caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Dosage:
HIV infection (in combination with other antiretroviral drugs), by mouth, ADULT 300 mg twice daily; CHILD 3 months–16 years, 8 mg/kg twice daily (maximum 600 mg daily)
Adverse effects:
hypersensitivity reactions (see above), nausea, vomiting, diarrhoea, anorexia, lethargy, fatigue, fever, headache, pancreatitis, lactic acidosis (see hepatic disease, above); rash and gastrointestinal disturbances more common in children

DIDANOSINE

ddi, DDI
Chewable tablets; didanosine (with calcium and magnesium antacids) 25 mg, 50 mg, 150 mg, 200mg
Oral solution (Powder for oral solution), didanosine (with calcium and magnesium antacids) 100 mg/sachet, 167 mg/sachet, 250 mg/sachet

NOTE.
Antacids in formulation may affect absorption of other drugs—see interactions: Appendix 1 (antacids)

HIV infection in combination with at least two other antiretroviral drugs

Precautions:
history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Adverse effects); history of liver disease (see below); renal and hepatic impairment (see Appendices 4 and 5); pregnancy and breastfeeding (see notes above); dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur; interactions: Appendix 1

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 therefore caution in liver disease, excessive alcohol intake, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis
Dosage:
HIV infection (in combination with other antiretroviral drugs), by mouth, ADULT under 60 kg 250 mg daily in 1–2 divided doses, body weight over 60 kg 400 mg daily in 1–2 divided doses; CHILD under 3 months, 50 mg/m² twice daily; 3 months–13 years, 90 mg/m² twice daily or 240 mg/m² once daily

Patient Advice.
To ensure sufficient antacid from tablets containing antacid, each dose to be taken as 2 tablets (CHILD under 1 year 1 tablet) chewed thoroughly, crushed or dispersed in water; tablets should be taken at least 1 hour before food or on an empty stomach

Adverse effects:
pancreatitis (see also under Precautions); peripheral neuropathy especially in advanced HIV infection–suspend (reduced dose may be tolerated when symptoms resolve); hyperuricemia (suspend treatment if significant elevation); diarrhoea (occasionally serious); also reported, nausea, vomiting, dry mouth, asthenia, headache, hypersensitivity reactions, retinal and optic nerve changes (especially in children), diabetes mellitus, raised liver enzymes (see also under Precautions), liver failure

LAMIVUDINE

3TC
Tablets , lamivudine 150 mg
Oral solution, lamivudine 50 mg/5 ml

Uses:
HIV infection in combination with at least two other antiretroviral drugs

Precautions:
renal impairment (Appendix 4), hepatic disease (see below); pregnancy and breastfeeding (see notes above); interactions: Appendix 1

HEPATIC DISEASE.
Potentially life-threatening lactic acidosis and severe hepato-megaly with steatosis reported therefore caution (particularly in obese women) in liver disease, liver enzyme abnormalities, or risk factors for liver disease; suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis. Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine

Dosage:
HIV infection (in combination with other antiretroviral drugs), by mouth , ADULT 150 mg twice daily or 300 mg once daily; INFANT under 1 month, 2 mg/kg twice daily; CHILD 1 month or over, 4 mg/kg twice daily (maximum 300 mg daily)

Adverse effects:
6.7 Antiprotozoal drugs 225

nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia and red-cell aplasia; lactic acidosis; raised liver enzymes and serum amylase reported

**STAVUDINE**

*d4T*

Capsules, stavudine 30 mg,

Oral solution (Powder for oral solution), stavudine 5 mg/5 ml

**Uses:**

HIV infection in combination with at least two other antiretroviral drugs

**Precautions:**

history of peripheral neuropathy (see below); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; hepatic disease (see below); renal impairment (Appendix 4); pregnancy and breastfeeding (see notes above);

**interactions:** Appendix 1

**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

**HEPATIC DISEASE.**

Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

**Dosage:**

HIV infection (in combination with other antiretroviral drugs), by mouth, ADULT under 60 kg, 30 mg twice daily preferably at least 1 hour before food; body weight over 60 kg, 40 mg twice daily; CHILD over 3 months, under 30 kg, 1 mg/kg twice daily; body weight over 30 kg, 30 mg twice daily

**Adverse effects:**

peripheral neuropathy (dose-related, see above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes (see hepatic disease, above) and serum amylase; neutropenia;

thrombocytopenia

ZIDOVUDINE

Azidothymidine, AZT, ZDV

NOTE.
The abbreviation AZT which has sometimes been used for zidovudine has also been used for another drug

Syrup (Oral solution), zidovudine 50 mg/5 ml

Uses:
HIV infection in combination with at least two other antiretroviral drugs; monotherapy for prevention of maternal-fetal HIV transmission (but see notes above under Pregnancy)

Contraindications:
abnormally low neutrophil counts or haemoglobin (consult product literature); neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase (consult product literature)

Precautions:
haematological toxicity; vitamin B₁₂ deficiency (increased risk of neutropenia); reduce dose or interrupt treatment according to product literature if anaemia or myelosuppression; renal impairment (Appendix 4); hepatic impairment (see below and Appendix 5); risk of lactic acidosis, (see below); elderly; pregnancy and breastfeeding (see notes above); interactions: Appendix 1

HEPATIC DISEASE.
Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women), suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Dosage:
HIV infection (in combination with other antiretroviral drugs), by mouth, ADULT 500–600 mg daily in 2–3 divided doses; INFANT under 4 weeks, 4 mg/kg twice daily; CHILD 4 weeks–13 years 180 mg/m² twice daily
Patients temporarily unable to take zidovudine by mouth, by intravenous infusion over 1 hour, adult 1–2 mg/kg every 4 hours (approximating to 1.5–3 mg/kg every 4 hours by mouth) usually for not more than 2 weeks; child 80–160 mg/m² every 6 hours (120 mg/m² every 6 hours approximates to 180 mg/m² every 6 hours by mouth)
Prevention of maternal-fetal HIV transmission, see notes above under Pregnancy

ADMINISTRATION AND DILUTION.
According to manufacturer’s directions00

Adverse effects:
anæmia (may require transfusion), neutropenia, and leukopenia (all more frequent with high dose and advanced disease); also nausea and vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised bilirubin and liver enzymes (see hepatic disease, above); chest pain, dyspnoea, cough; influenza-like symptoms, headache, fever, paraesthesia, neuropathy, convulsions, dizziness, somnolence, insomnia, anxiety, depression, loss of mental acuity, malaise, anorexia, asthenia, myopathy, myalgia; pancytopenia, thrombocytopenia; gynaecomastia; urinary frequency; rash, pruritus, pigmentation of nail, skin and oral mucosa

Lamivudine/Zidovudine

Tablet lamivudine 150mg / zidovudine 300mg, 
Dose: 1 tablet every 12 hoursTablet zidovudine 300mg, lamivudine 150mg x 60-tab pack 
Dose: 1 tablet every 12 hours

Non-nucleoside reverse transcriptase inhibitors

In some settings it may not be possible to carry out full monitoring described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also notes above) 

EFAVIRENZ

EFV, EFZ

Capsules, efavirenz 600 mg
Oral solution, efavirenz 150 mg/5 ml

Uses:
HIV infection in combination with at least two other antiretroviral drugs

Contraindications:
pregnancy (see notes above and Appendix 2; substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured)

Precautions:
hepatic impairment (avoid if severe; Appendix 5); severe renal impairment (Appendix 4); breastfeeding (see notes above); elderly; history of mental illness or substance abuse; interactions: Appendix 1

RASH.
Rash, usually in the first 2 weeks, is the most common adverse effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—rash usually resolves within 1
month

Dosage:
HIV infection (in combination with other antiretroviral drugs), by mouth. **ADULT** 600 mg once daily; **CHILD** over 3 years, body weight 10–15 kg, 200 mg once daily; body weight 15–19 kg, 250 mg once daily; body weight 20–24 kg, 300 mg once daily; body weight 25–32 kg, 350 mg once daily; body weight 33–39 kg, 400 mg once daily; body weight 40 kg and over, adult dose.

Adverse effects:
rash including Stevens-Johnson syndrome (see also above); dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration (administration at bedtime especially in the first 2–4 weeks reduces CNS effects); nausea; less frequently vomiting, diarrhoea, hepatitis, depression, anxiety, psychosis, amnesia, ataxia, stupor, vertigo; also reported raised serum cholesterol, elevated liver enzymes (especially if seropositive for hepatitis B or C), pancreatitis.

NEVIRAPINE

NVP
Tablets, nevirapine 200 mg
Oral suspension, nevirapine 50 mg/5 ml
Uses:
HIV infection, in combination with at least two other antiretroviral drugs; prevention of mother-to-child transmission in HIV-infected patients (but see notes above under Pregnancy)

Precautions:
hepatic impairment (see below and Appendix 5); history of chronic hepatitis (greater risk of hepatic adverse effects), pregnancy and breastfeeding (see notes above); interactions: Appendix 1

HEPATIC DISEASE.
Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually occurring in first 8 weeks; monitor liver function before long-term treatment then every 2 weeks for 2 months then after 1 month and then every 3–6 months; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction

RASH.
Rash, usually in first 8 weeks, is most common adverse effect; incidence reduced if introduced at low dose and dose increased gradually; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, swelling, 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 should be told how to recognize hypersensitivity reactions and advised to seek immediate medical attention if symptoms develop

**Dosage:**
HIV infection (in combination with other antiretroviral drugs), by mouth, ADULT 200 mg once daily for first 14 days then (if no rash present) 200 mg twice daily; INFANT 15–30 days old, 5 mg/kg once daily for 14 days, then (if no rash present) 120 mg/m² twice daily for 14 days, then 200 mg/m² twice daily; CHILD 1 month–13 years, 120 mg/m² twice daily for first 14 days, then (if no rash present) 200 mg/m² twice daily

Prevention of mother-to-child transmission of HIV (see also notes above under Pregnancy), by mouth, ADULT 200 mg as a single dose at onset of labour; NEONATE 2 mg/kg as a single dose within 72 hours of birth

**NOTE.** If treatment interrupted for more than 7 days reintroduce with 200 mg daily (INFANT 15–30 days old, 5 mg/kg; CHILD over 1 month, 120 mg/m²) and increase dose cautiously

**Adverse effects:** rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis (see also Precautions above); hepatitis or jaundice reported (see also Precautions above); nausea, vomiting, abdominal pain, diarrhoea, headache, drowsiness, fatigue, fever; hypersensitivity reactions (may involve hepatic reactions and rash, see Precautions above); anaphylaxis, angioedema, urticaria also reported

**Protease inhibitors**
In some settings it may not be possible to carry out full monitoring described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also notes above)

**INDINAVIR**

**IDV**
*Capsules*, indinavir (as sulfate) 400 mg

**Uses:**
HIV infection in combination with two nucleoside reverse transcriptase inhibitors and usually with low-dose ritonavir booster
Precautions:
hepatic impairment (Appendix 5); ensure adequate hydration to reduce risk of nephrolithiasis; diabetes mellitus; haemophilia; pregnancy (see notes above and Appendix 2); breastfeeding (see notes above); metabolism of many drugs inhibited if administered concomitantly; interactions: Appendix 1

Dosage:
HIV infection (in combination with nucleoside reverse transcriptase inhibitors and low-dose ritonavir booster), by mouth, ADULT indinavir 800 mg and ritonavir 100 mg both twice daily
HIV infection (in combination with nucleoside reverse transcriptase inhibitors but without ritonavir booster), by mouth, ADULT 800 mg every 8 hours; CHILD and ADOLESCENT 4–17 years, 500 mg/m$^2$ every 8 hours (maximum 800 mg every 8 hours); CHILD under 4 years, safety and efficacy not established

Patient Advice.
Administer 1 hour before or 2 hours after a meal; may be administered with low-fat, light meal; when given with didanosine tablets, allow 1 hour between the drugs (antacids in didanosine reduce absorption of indinavir)

Adverse effects:
nausea, vomiting, diarrhoea, abdominal discomfort, dyspepsia, flatulence, pancreatitis, dry mouth, taste disturbances; headache, dizziness, insomnia; myalgia, myositis, rhabdomyolysis, asthenia, hypoaesthesia, paraesthesia; hyperglycaemia; anaphylactoid reactions, rash (including Stevens-Johnson syndrome), pruritus, dry skin, hyperpigmentation, alopecia, paronychia; interstitial nephritis, nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children); hepatitis, transient hyperbilirubinaemia; blood disorders including neutropenia, haemolytic anaemia; lipodystrophy and metabolic effects, see notes above

LOPINAVIR WITH RITONAVIR

LPV/r
Capsules, lopinavir 133.3 mg and ritonavir 33.3 mg
Oral solution, lopinavir 400 mg and ritonavir 100 mg/5 ml
NOTE.
5 ml oral solution = 3 capsules; where appropriate capsules may be used instead of oral solution; oral solution excipients include propylene glycol and alcohol 42%

Uses:
HIV infection in combination with two other antiretroviral drugs
NOTE.
Ritonavir increases effect of lopinavir (see notes above); low dose in combination does not have intrinsic antiviral activity

**Precautions:**
hepatic impairment—avoid if severe (Appendix 5); renal impairment (Appendix 4); haemophilia; pregnancy (see notes above and Appendix 2); breastfeeding (see notes above and Appendix 3); diabetes mellitus; oral solution contains propylene glycol—avoid in hepatic and renal impairment, and in pregnancy, increased susceptibility to propylene glycol toxicity in slow metabolizers; **interactions:** Appendix 1

**PANCREATITIS.**
Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated—discontinue if pancreatitis diagnosed

**Dosage:**
HIV infection (in combination with other antiretroviral drugs), by mouth, **ADULT** and **ADOLESCENT** with body surface area of 1.3 m² or greater, 3 capsules or 5 ml twice daily (lopinavir 400 mg and ritonavir 100 mg twice daily); **CHILD** 6 months–13 years, lopinavir 225 mg/m² and ritonavir 57.5 mg/m² twice daily (or body weight 7–15 kg lopinavir 12 mg/kg and ritonavir 3 mg/kg twice daily, body weight 15–40 kg lopinavir 10 mg/kg and ritonavir 5 mg/kg twice daily)

**NOTE.**
Increase dose by 33% if used with efavirenz or with nevirapine

**Patient Advice.**
Each dose to be taken with food

**Adverse effects:**
diarrhoea, nausea, vomiting, colitis, abdominal discomfort, asthenia, headache, insomnia; rash; less frequently, dry mouth, hepatic dysfunction, pancreatitis (see also Precautions), dyspepsia, dysphagia, oesophagitis, influenza-like syndrome, appetite changes; hypertension, palpitations, thrombophlebitis, vasculitis, chest pain, dyspnoea, agitation, anxiety, ataxia, hypertonia, confusion, depression, dizziness, dyskinesia, paraesthesia, peripheral neuritis, somnolence; Cushing syndrome, hypothyroidism, sexual dysfunction, anaemia, leukopenia, dehydration, oedema, lactic acidosis; arthralgia, myalgia, abnormal vision, otitis media, taste disturbances, tinnitus; acne, alopecia, dry skin, pruritus, skin discoloration, nail disorders, sweating; lipodystrophy and metabolic effects (see notes above); raised bilirubin and lowered sodium, low platelet and low neutrophil counts also reported in children

**RITONAVIR**

RTV
*Capsules,* ritonavir 100 mg
*Oral solution,* ritonavir 400 mg/5 ml

**Uses:**
HIV infection, as a booster to increase effect of indinavir, lopinavir or saquinavir and in combination with two other antiretroviral drugs

**Contraindications:**
Severe hepatic impairment

**Precautions:**
Hepatic impairment; diabetes mellitus; haemophilia; pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

**PANCREATITIS.**
Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated—discontinue if pancreatitis diagnosed

**Dosage:**
HIV infection (as a booster with other antiretroviral drugs), by mouth, **ADULT** 100 mg twice daily; **CHILD** 6 months–13 years 57.5 mg/m² twice daily (or 3–5 mg/kg twice daily) (maximum 100 mg twice daily)

**Adverse effects:**
nausea, vomiting, diarrhoea (may impair absorption—close monitoring required), abdominal pain, taste disturbances, dyspepsia, anorexia, throat irritation; vasodilatation; headache, circumoral and peripheral paraesthesia, hyperaesthesia, dizziness, sleep disturbances, asthenia, rash, hypersensitivity reactions, leukopenia; raised liver enzymes, bilirubin, and uric acid; occasionally flatulence, eructation, dry mouth and ulceration, cough, anxiety, fever, pain, myalgia, weight loss, decreased thyroxine, sweating, pruritus, electrolyte disturbances, anaemia, neutropenia, increased prothrombin time; pancreatitis (see also Pancreatitis, above); lipodystrophy and metabolic effects, see notes above
6.7 Antiprotozoal drugs
6.7 Antiprotozoal drugs
Section 7: Antimigraine drugs

7.1 Acute migraine attack
7.2 Migraine prophylaxis
Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be initiated for migraine. Untreated, migraine attacks last for several hours and sometimes for as long as 3 days. Migraine headache is frequently accompanied by episodes of gastrointestinal disturbance including nausea and vomiting. The headache may be preceded or accompanied by aura (classical migraine) which is characterised by visual disturbances such as flickering lines and fragmented vision or sensory disturbances such as tingling or numbness; rarely, hemiparesis or impaired consciousness may occur. Migraine without aura (common migraine) is the more common form occurring in about 75% of patients who experience migraine. Emotional or physical stress, lack of or excess sleep, missed meals, menstruation, alcohol and specific foods including cheese and chocolate are often identified as precipitating factors; oral contraceptives may increase the frequency of attacks. Avoidance of such precipitating factors can be of great benefit in preventing or reducing the frequency of attacks and should be addressed in detail. Women taking combined oral contraceptives who experience an onset or increase in frequency of headaches should be advised of other contraceptive measures.

The two principal strategies of migraine management are treatment of acute attacks and prophylactic treatment.

7.1 Acute migraine attack

Treatment of acute attacks may be non-specific using simple analgesics, or specific using an ergot alkaloid such as ergotamine. If nausea and vomiting are features of the attack, an antiemetic drug may be given. Treatment is generally by mouth; some drugs are available as suppositories which may be administered if the oral route is not effective (poor oral bioavailability, or absorption from the gut impaired by vomiting) or not practicable (patient unable to take drugs orally). Simple analgesics including NSAIDs (nonsteroidal anti-inflammatory drugs) can be effective in mild to moderate forms of migraine if taken early in the attack; most migraine headaches respond to paracetamol. Peristalsis is often reduced during migraine attacks and, if available, a dispersible or effervescent preparation of the drug is preferred because of enhanced absorption compared with a conventional tablet. The risk of Reye syndrome due to acetylsalicylic acid in children can be avoided by giving paracetamol instead. Frequent and prolonged use of analgesics by migraine sufferers may lead to analgesic-induced headache. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound.
such as a **5HT1 agonist (Triptan)**.

**Ergotamine** should be considered only when attacks are unresponsive to non-opioid analgesics. It is poorly absorbed when taken orally or sublingually. Rectal suppositories may offer an advantage when other routes of administration are unsatisfactory. To be fully effective ergotamine must be taken in adequate amounts as early as possible during each attack. Adverse effects limit how much ergotamine can be used in a single attack and consequently the recommended dosage should never be exceeded, and at least four days should elapse between successive treatments. Even normal dosage can lead to dependence, tolerance to adverse effects and to a withdrawal syndrome on discontinuing the drug. To avoid dependence the frequency of administration should be limited to no more than twice a month. Adverse effects include nausea, vomiting, diarrhoea and vertigo; chronic ergotism is characterized by severe peripheral vasoconstriction which can lead to gangrene in the extremities. The severity of adverse effects prevents the use of ergotamine for migraine prophylaxis.

**Analgesics**

**PARACETAMOL**

*Tablets*, paracetamol, 500 mg

**Uses:**
Acute migraine attacks, tension headache; mild to moderate pain, pyrexia (section 2.1.2)

**Precautions:**
Hepatic impairment (Appendix 5); renal impairment; alcohol dependence; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **overdosage:** section 4.2.1; **interactions:** Appendix 1

**Dosage:**
Treatment of acute migraine attack, by **mouth**, **ADULT** 0.5–1 g at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 g daily; **CHILD** 6–12 years 250–500 mg at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours

Treatment of acute migraine attack, by **rectum**, **ADULT** and **CHILD** over 12 years 0.5–1 g at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours; **CHILD** 6–12 years 250–500 mg at first sign of attack, may be repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours

**Adverse effects:**
Rare, but rashes, blood disorders; **important:** liver damage (and less frequently renal damage) following overdosage

Ergot alkaloid
ERGOTAMINE TARTRATE

Drug subject to international control under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988)

*Tablets*, ergotamine tartrate 1 mg

**Uses:**
Treatment of acute migraine attacks unresponsive to analgesics

**Contraindications:**
pregnancy (Appendix 2) and breastfeeding (Appendix 3); children; peripheral vascular disorders, coronary artery disease, oblitative vascular disease and Raynaud syndrome, severe hypertension, sepsis; severe renal or hepatic dysfunction (Appendices 4 and 5); hyperthyroidism; porphyria

**Precautions:**
Elderly; daily rebound headaches indicative of ergotamine dependence; discontinuation after regular normal dosage may result in withdrawal headache; risk of peripheral vasospasm (advise patient to stop medication immediately if numbness or tingling in extremities or anginal pain develops and to contact doctor); **interactions:** Appendix 1

**Dosage:**
Treatment of acute migraine attack, *by mouth or by rectum*,

**ADULT**
1–2 mg at first sign of attack, maximum 4 mg in 24 hours; do not repeat at intervals of less than 4 days, maximum 8 mg in any one week; not to be used more than twice in any 1 month; **CHILD** not recommended

**Adverse effects:**
nausea, vomiting, vertigo, abdominal pain, diarrhoea, muscle cramps, increased headache; precordial pain, myocardial ischaemia; rarely myocardial infarction; repeated high dosage may cause ergotism with gangrene and confusion; pleural and peritoneal fibrosis may occur with excessive use

5HT1 Agonist

SUMATRIPTAN

*Tablets*, 50mg

**Use**
Acute treatment of cluster headache episodes

**Precautions**
Sumatriptan is only indicated in patients e” 18yrs of age with a clear diagnosis of migraine or cluster headaches; cardiac events (coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest and death), cerebral/subarachnoid hemorrhage, and

stroke have been reported with 5-HT1 agonist action. Do not give to patients with risk factors for CAD. Significant elevation of blood pressure, including hypertension crisis. Use in caution in patients with history of seizure disorder.

**Adverse effects**

Dizziness, chest pain or tightness, drowsiness, warm/cold sensation, nausea

**Dosage**

**ADULTS**, oral: a single dose of 25mg, 50mg, or 100mg (taken with fluids), if unsatisfactory results have not been obtained after two hours, a second dose may be administered

### 7.2 Migraine prophylaxis

Prophylactic treatment should be considered for patients in whom treatment of acute migraine attacks with analgesics or ergotamine is ineffective, or in whom attacks occur more than once a month, or for those with less frequent but severe or prolonged attacks. Prophylaxis can reduce the severity and frequency of attacks but does not eliminate them completely; additional symptomatic treatment is still needed. However, long-term prophylaxis is undesirable and treatment should be reviewed at 6-monthly intervals. Of the many drugs that have been advocated beta-adrenoceptor antagonists (beta-blockers) are most frequently used. **Propranolol**, a non-selective beta-blocker and other related compounds with similar profile such as **atenolol** are generally preferred. The potential for beta-blockers to interact with ergotamine should be borne in mind. Tricyclic antidepressants, such as **amitriptyline** (section 24.2.1) or calcium-channel blocking drugs such as **verapamil** (section 12.1) may be of value.

**PROPRANOLOL HYDROCHLORIDE**

Propranolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives

**Tablets**, propranolol hydrochloride 20 mg, 40 mg

**Uses:**

Prophylaxis of migraine

**Contraindications:**

asthma or history of obstructive airways disease, uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma

**Precautions:**

first-degree atrioventricular block; renal impairment (Appendix 4); liver disease (Appendix 5); pregnancy and breastfeeding
(Appendices 2 and 3); portal hypertension; diabetes mellitus; myasthenia gravis; history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); interactions: Appendix 1

**Dosage:**
Prophylaxis of migraine, *by mouth* **ADULT** initially 40 mg 2–3 times daily, increased by same amount at weekly intervals if necessary; usual range 80–160 mg daily; **CHILD** under 12 years, 20 mg 2–3 times daily

**Adverse effects:**
bradycardia, heart failure, hypotension, conduction disorders, bronchospasm, peripheral vasoconstriction, exacerbation of intermittent claudication and Raynaud phenomenon, gastrointestinal disturbances, fatigue, sleep disturbances including nightmares; rarely, rash, dry eyes (reversible), exacerbation of psoriasis
SECTION 8:
ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE DRUGS AND DRUGS USED IN PALLIATIVE CARE

8.1 Immunosuppressive medicines
8.2 Cytotoxic medicines
8.3 Hormones and antihormones
8.4 Medicines used in palliative care
Antineoplastic and immunosuppressive drugs and drugs used in palliative care

8.1 Immunosuppressive drugs

**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 or 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** is the most widely used drug in transplant recipients. It is useful when corticosteroid therapy alone has proven inadequate or for other conditions when a reduction in the dose of concurrently administered corticosteroids is required. It is metabolized to mercaptopurine and, as with mercaptopurine, doses need to be reduced when given with allopurinol. The predominant toxic effect is myelosuppression, although hepatic toxicity also occurs.

**Ciclosporin** is a potent immunosuppressant which is virtually free of myelotoxic effects, but is markedly nephrotoxic. It is particularly useful for the prevention of graft rejection and for the prophylaxis of graft-versus-host disease. The dose is adjusted according to plasma-ciclosporin concentrations and renal function. Dose-related increases in serum creatinine and blood urea nitrogen (BUN) during the first few weeks may necessitate dose reduction.

Corticosteroids such as **prednisolone** (section 8.3) have significant immunosuppressant activity and can also be used to prevent rejection of organ transplants.

**Azathioprine**

Azathioprine is a complementary immunosuppressive drug

**Tablets,** azathioprine 50 mg

**Injection (Powder for solution for injection),** azathioprine (as sodium salt), 100-mg vial

**Uses:**
to prevent rejection in transplant recipients; rheumatoid arthritis (section 2.4); inflammatory bowel disease (section 17.4)

**Contraindications:**

Hypersensitivity to azathioprine and mercaptopurine; breast-feeding (Appendix 3)

**Precautions:**
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; reduce dose in elderly; pregnancy (Appendix 2); renal impairment (Appendix 4); liver disease (Appendix 5); **interactions:** Appendix 1

**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

**Dosage:**
Transplant rejection, *by mouth or by intravenous injection* (over at least 1 minute and followed by 50 ml sodium chloride intravenous infusion) *or by intravenous infusion*, ADULT up to 5 mg/kg on day of surgery, then reduced to 1–4 mg/kg daily according to response for maintenance

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer’s directions

**Note.**
Intravenous injection is alkaline and very irritant; the intravenous route should therefore **only** be used if oral administration is not possible

**Adverse effects:**
hypersensitivity reactions including malaise, dizziness, vomiting, fever, muscular pains, arthralgia, rash, hypotension or interstitial nephritis call for immediate withdrawal; haematological toxicity includes leukopenia and thrombocytopenia (reversible upon withdrawal); liver impairment, cholestatic jaundice; hair loss; increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, hepatic veno-occlusive disease

**CICLOSPORIN**
Ciclosporin is a complementary immunosuppressive drug

**Capsules**, ciclosporin 25 mg

**Concentrate for infusion** (Concentrate for solution for infusion), ciclosporin 50 mg/ml, 1-ml ampoule

**Uses:**
rejection in kidney, liver, heart or bone-marrow transplantation; graft-versus-host disease

**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, also Appendix 4); monitor liver function (adjust dosage according to bilirubin and liver enzymes, also Appendix 5); 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; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:

Note.
Lower doses are required when ciclosporin is used with other immunosuppressants

Organ transplantation, by mouth, ADULT and CHILD over 3 months 10–15 mg/kg 4–12 hours before surgery, then 10–15 mg/kg daily for 1–2 weeks, reducing to 2–6 mg/kg daily for maintenance (adjust dose according to blood concentration and kidney function)

Organ transplantation, by intravenous infusion over 2–6 hours, ADULT and CHILD one-third of the corresponding dose by mouth

Bone marrow transplantation, graft-versus-host disease, by mouth, ADULT and CHILD over 3 months 12.5–15 mg/kg daily for 2 weeks, starting on day before surgery, followed by 12.5 mg/kg daily for 3–6 months, then gradually tailed off (may take up to 1 year after transplant)

Bone marrow transplantation, graft-versus-host disease, by intravenous infusion over 2–6 hours, ADULT and CHILD over 3 months 3–5 mg/kg daily for 2 weeks, starting on day before surgery, followed by maintenance by mouth

CONVERSION.

Any conversion between brands should be undertaken very carefully, and the manufacturer consulted for further information

DILUTION AND ADMINISTRATION.

According to manufacturer’s directions

Note.
Concentrate for infusion contains polyethoxylated castor oil, which has been associated with anaphylaxis; observe patient for 30 minutes after starting infusion, and then at frequent intervals

Adverse effects:

dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection; 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

8.2 Cytotoxic (antineoplastic) drugs

incidence of malignancies and lymphoproliferative disorders; increased susceptibility to infections due to immunosuppression; gastrointestinal disturbances; gingival hyperplasia; hirsutism; fatigue; allergic reactions; thrombocytopenia (sometimes with haemolytic uraemic syndrome); also mild anaemia, tremors, convulsions, neuropathy; dysmenorrhoea or amenorrhoea; pancreatitis, myopathy or muscle weakness; cramp; gout; oedema; headache

8.2 Cytotoxic (antineoplastic) drugs

Note.

WHO advises that adequate resources and specialist supervision are a prerequisite for the introduction of this class of drugs. Specific expertise, diagnostic precision, individualization of dosage or special equipment are required for their proper use. The treatment of cancer with drugs, radiotherapy and surgery is complex and should only be undertaken by an oncologist. For this reason, the following information is provided merely as a guide. Chemotherapy may be curative or used to alleviate symptoms or to prolong life. Where 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 many malignancies a combination of drugs provides the best response. Examples of combination therapy include:

- ‘CHOP’ (cyclophosphamide, doxorubicin, vincristine, prednisolone) for non-Hodgkin disease;
- ‘ABVD’ (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin disease;
- MOPP’ (chlormethine, vincristine, procarbazine, prednisolone) for Hodgkin disease.

Cytotoxic drugs are often combined with other classes of drugs (section 8.3) in the treatment of malignant conditions. Such drugs include hormone agonists and antagonists, corticosteroids and immunostimulant drugs. Combinations are, however, more toxic than single drugs.

The following information covers drugs that have specific anti-tumour activity. However, they are toxic drugs which should be used with great care and monitoring. The specific doses and details of contraindications, precautions and adverse effects for cytotoxic drugs have been omitted from this section since treatment should be undertaken by specialists using agreed regimens. Health authorities may wish to formulate their own regimens on the basis of expert advice.

PRECAUTIONS AND CONTRAINDICATIONS

Treatment with cytotoxic drugs should be initiated only after...
baseline tests of liver and kidney function have been performed and baseline blood counts established. It may be necessary to modify or delay treatment in certain circumstances. The patient should also be monitored regularly during chemotherapy and cytotoxic drugs withheld if there is significant deterioration in bone-marrow, liver or kidney function.

Many cytotoxic drugs are teratogenic and should not be administered during pregnancy especially in the first trimester. Contraceptive measures are required during therapy and possibly for a period after therapy has ended. Cytotoxic drugs are also contraindicated during breastfeeding.

Cytotoxic drugs should be administered with care to avoid undue toxicity to the patient or exposure during handling by the health care provider. Local policies for the handling and reconstitution of cytotoxic drugs should be strictly adhered to; also all waste, including patient's body fluids and excreta (and any material contaminated by them) should be treated as hazardous.

Extravasation of intravenously administered cytotoxic drugs can result in severe pain and necrosis of surrounding tissue. If extravasation occurs, aspiration of the drug should first be attempted, then the affected limb is elevated and warm compresses applied to speed and dilute the infusion or it is localized by applying cold compresses until the inflammation subsides; in severe cases, hydrocortisone cream may be applied topically to the site of inflammation. The manufacturer’s literature should also be consulted for more specific information.

ADVERSE EFFECTS

Cytotoxic drugs have a considerable potential to damage normal tissue. Specific adverse effects apply, but a number of effects are common to all cytotoxics such as bone-marrow and immunological suppression. Furthermore, the concomitant use of immunosuppressive drugs will enhance susceptibility to infections. Fever associated with neutropenia or immunosuppression requires immediate treatment with antibiotics.

**Nausea and vomiting.**

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). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Cytotoxic drugs associated with a low risk of emesis include etoposide, fluorouracil, low-dose methotrexate, and the vinca alkaloids; those with an intermediate risk include low-dose cyclophosphamide, doxorubicin, and high-dose methotrexate; and the highest risk is with cisplatin, high-dose cyclophosphamide, and dacarbazine.
For patients at a low risk of emesis, pretreatment with an oral phenothiazine (for example chlorpromazine, section 24.1), continued for up to 24 hours after chemotherapy, is often helpful. For patients at a higher risk dexamethasone 6–10 mg by mouth (section 18.1) may be added before chemotherapy. For patients at a high risk of emesis or when other therapies are ineffective, high doses of intravenous metoclopramide (section 17.2) may be used.

**NOTE.**

High doses of metoclopramide are preferably given by continuous intravenous infusion: an initial dose of 2–4 mg/kg is given over 15 to 20 minutes, followed by a maintenance dose of 3–5 mg/kg over 8 to 12 hours; the total dose should not exceed 10 mg/kg in 24 hours.

Dexamethasone is the drug of choice for the prevention of delayed symptoms; it is used alone or with metoclopramide. Good symptom control is the best way to prevent anticipatory symptoms and the addition of diazepam to antiemetic therapy is helpful because of its sedative, anxiolytic and amnesic effects.

**Hyperuricaemia.** 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 (section 2.3.2) initiated 24 hours before cytotoxic treatment and continued for 7 to 10 days afterwards.

**Alopecia.** Alopecia is common during treatment with cytotoxic drugs. There is no drug treatment, but the condition often reverses spontaneously once treatment has stopped.

**ALKYLATING DRUGS**

Alkylating drugs are among the most widely used drugs in cancer chemotherapy. They act by damaging DNA and therefore interfering with cell replication. However, there are two complications. Firstly, they affect gametogenesis and may cause permanent male sterility; in women, the reproductive span may be shortened by the onset of a premature menopause. Secondly, they are associated with a marked increase in the incidence of acute non-lymphocytic leukaemia, in particular when combined with extensive radiation therapy.

**Cyclophosphamide** requires hepatic activation; it can therefore be given orally and is not vesicant when given intravenously. Like all alkylating drugs its major toxic effects are myelosuppression, alopecia, nausea and vomiting. It can also cause haemorrhagic cystitis; an increased fluid intake for 24 to 48 hours will help to avoid this complication. Cyclophosphamide...
is used either as part of treatment or as an adjuvant in non-Hodgkin lymphomas, breast cancer, childhood leukaemia, and ovarian cancer. It is also used in several palliative regimens.

CYCLOPHOSPHAMIDE

Cyclophosphamide is a complementary cytotoxic drug

**Tablets, cyclophosphamide 25 mg**

**Injection (Powder for solution for injection), cyclophosphamide 500-mg vial**

**Uses:**
malignant lymphomas including non-Hodgkin lymphomas, lymphocytic lymphoma, Burkitt lymphoma; multiple myeloma; leukaemias, mycosis fungoides; neuroblastoma; adenocarcinoma of the ovary; retinoblastoma; breast cancer

**Contraindications:**
see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

**Precautions:**
See notes above and consult specialist literature; renal impairment (Appendix 4) and hepatic impairment (Appendix 5);

**Dosage:**
Consult specialist literature

**Adverse effects:**
See notes above and consult specialist literature

ANTIMETABOLITES AND RELATED THERAPY

**Fluorouracil** is primarily used in the adjuvant treatment of colorectal and breast cancer. It is also employed in the palliative treatment of other malignancies. It causes myelosuppression and the palmar-plantar syndrome (erythema and painful desquamation of the hands and feet). When its action is modified by other drugs (such as calcium folinate), its toxicity profile can change; mucositis and diarrhoea may be significant problems. Central neurotoxicity can also occur.

**Methotrexate** is used to treat a variety of malignancies and it plays a major role as an adjuvant for the treatment of breast cancer. Like fluorouracil, methotrexate is myelotoxic, but nausea and vomiting are minimal. It also causes mucositis. Renal impairment reduces methotrexate excretion and can exacerbate toxicity.

**FLUOROURACIL**
5–fluorouracil, 5FU

Fluorouracil is a complementary cytotoxic drug
Injection (Solution for injection), fluorouracil 50 mg/ml, 5-ml ampoule  

**Uses:**
carcinomas of the colorectum, breast, stomach, pancreas, cervix, prostate, ovary and endometrium; liver tumours; head and neck tumours; actinic keratosis (section 13.5)  

**Contraindications:**
see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)  

**Precautions:**
see notes above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1  

**Dosage:**
Consult specialist literature  

**Adverse effects:**
see notes above and consult specialist literature  

**METHOTREXATE**

Methotrexate is a complementary cytotoxic drug  

**Tablets,** methotrexate 2.5 mg  

**Injection (Solution for injection),** methotrexate (as sodium salt) 25mg/ml, 2-ml vial  

**Uses:**
carcinoma of the breast, head and neck, and lung; trophoblastic tumours; acute lymphoblastic leukaemia, meningeal leukaemia; non-Hodgkin lymphomas; advanced cases of mycosis fungoides; non-metastatic osteosarcoma; severe rheumatoid arthritis (section 2.4)  

**Contraindications:**
see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)  

**Precautions:**
see notes above and consult specialist literature; renal and hepatic impairment (Appendices 4 and 5); **interactions:** Appendix 1  

**Dosage:**
Consult specialist literature  

**Adverse effects:**
see notes above and consult specialist literature  

8.3 **Hormones and antihormones**

The corticosteroids **prednisolone,** **dexamethasone** and **hydrocortisone** are synthetic hormones given at pharmacological doses particularly for haematological malignancies. Although there is no evidence for therapeutic superiority, prednisolone is used more commonly than dexamethasone or hydrocortisone (section 3.1); prednisolone is an important component of cura-
tive regimens for lymphomas and childhood leukaemias and elsewhere it has a palliative role. However, chronic use leads to the development of a cushingoid syndrome.

**Tamoxifen** is an estrogen-receptor antagonist. Its important role in breast cancer is use after surgery and for palliative management in patients with advanced disease. When given at recommended doses, it has few adverse effects, although, it can induce uterine endometrial malignancies.

**Diethylstilbestrol**, a synthetic estrogen, is used to manipulate the hormonal environment in patients with hormone-sensitive tumours (for example breast and testes). It has few significant adverse effects in women but in men it causes gynaecomastia, and, more importantly, increases the risk of cardiovascular disease. For breast cancer diethylstilbestrol has been superseded by tamoxifen but it can be used for its anti-androgen effect in prostate cancer as an adjunct or for palliation.

**PREDNISOLONE**

Prednisolone is a representative corticosteroid. Various drugs can serve as alternatives. Prednisolone is a complementary drug for the treatment of malignant neoplasms.

**Uses:**
with antineoplastic drugs for acute lymphoblastic and chronic lymphocytic leukaemias, Hodgkin disease, and non-Hodgkin lymphomas; inflammatory and allergic reactions (sections 3.1 and 18.1); eye (section 21.2)

**Contraindications:**
Untreated bacterial, viral, and fungal infections; avoid live virus vaccines

**Precautions:**
monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentration throughout treatment; adrenal suppression during and for some months after withdrawal—intercurrent infection or surgery may require increased dose of corticosteroid (or temporary reintroduction if already withdrawn); quiescent amoebiasis, strongyloidiasis, or tuberculosis possibly reactivated; increased severity of viral infections, particularly chickenpox and measles—passive immunization with immunoglobulin required; hypertension, recent myocardial infarction, congestive heart failure; renal impairment; hepatic impairment (Appendix 5); diabetes mellitus; osteoporosis; glaucoma; severe psychosis, epilepsy; peptic ulcer; pregnancy (Appendix 2); breastfeeding (Appendix 3);

**interactions:** Appendix 1

**Dosage:**

Leukaemias and lymphomas, by mouth, ADULT initially up to 100 mg daily, then gradually reduced if possible to 20–40 mg daily; CHILD up to 1 year, initially up to 25 mg, then 5–10 mg; 2–7 years, initially up to 50 mg, then 10–20 mg; 8–12 years, up to 75 mg, then 15–30 mg

Adverse effects:
- gastrointestinal effects including dyspepsia, oesophageal ulceration, development of or aggravation of peptic ulcers, abdominal distension, acute pancreatitis; increased appetite and weight gain; adrenal suppression with high doses, leading to cushingoid symptoms (moon face, acne, bruising, abdominal striae, truncal obesity, muscle wasting); menstrual irregularities and amenorrhoea; hypertension; osteoporosis, with resultant vertebral collapse and long-bone fractures; avascular osteonecrosis; ophthalmic effects including glaucoma, subcapsular cataracts, exacerbation of viral or fungal eye infections; diabetes mellitus; thromboembolism; delayed tissue healing; myopathy, muscle weakness of arms and legs; depression, psychosis, epilepsy; raised intracranial pressure; hypersensitivity reactions

**TAMOXIFEN**

Tamoxifen is a complementary drug for the treatment of breast cancer

**Tablets,** tamoxifen (as citrate) 10 mg, 20 mg

**Uses:**
- adjuvant treatment of estrogen-receptor-positive breast cancer;
- metastatic breast cancer

**Contraindications:**
- pregnancy (exclude before treatment and advise non-hormonal contraception if appropriate, see also Appendix 2); breastfeeding (Appendix 3)

**Precautions:**
- monitor for endometrial changes (increased incidence of hyperplasia, polyps, and cancer); cystic ovarian swellings in premenopausal women; increased risk of thromboembolism when used with antineoplastic drugs; avoid in porphyria; interactions: Appendix 1

**Dosage:**
- Breast cancer, by mouth, ADULT 20 mg daily

**Adverse effects:**
- hot flushes; endometrial changes (symptoms such as vaginal bleeding and other menstrual irregularities, vaginal discharge, pelvic pain require immediate investigation); increased pain and hypercalcaemia with bony metastases; tumour flare; nausea and vomiting; liver enzyme changes (rarely cholestasis, hepatitis, hepatic necrosis); hypertriglyceridaemia (sometimes with pancreatitis); thromboembolic events; decreased platelet count; oedema; alopecia; rash; headache; visual disturbances includ-
ing corneal changes, cataracts, retinopathy; rarely interstitial pneumonitis, hypersensitivity reactions including angioedema, Stevens-Johnson syndrome, bullous pemphigoid

8.4 Drugs used in palliative care

**Note.**
The Expert Committee on the Selection and Use of Essential Medicines recommends that all the drugs mentioned in Cancer Pain Relief: with a Guide to Opioid Availability, 2nd edition. Geneva: WHO 1996 be considered essential. These drugs are included in the relevant sections of the Model List according to their therapeutic use, for example analgesics. Palliative care includes both pain relief and the symptomatic relief of conditions including dyspnoea, restlessness and confusion, anorexia, constipation, pruritus, nausea and vomiting, and insomnia. Health authorities should be encouraged to develop their own palliative care services.

Pain relief can be achieved with drugs and neurosurgical, psychological and behavioural approaches adapted to individual patient needs. If carried out correctly, most patients with cancer pain can obtain effective relief. Pain is best treated with a combination of drug and non-drug measures. Some types of pain respond well to a combination of a non-opioid and an opioid analgesic. Other types of pain are relieved by combining a corticosteroid and an opioid. Neuropathic pains often show little response to non-opioids and opioids, but may be eased by tricyclic antidepressants and anticonvulsants (see below). Cancer patients often have many fears and anxieties, and may become depressed. Very anxious or deeply depressed patients may need an appropriate psychotropic drug in addition to an analgesic. If this fact is not appreciated, the pain may remain intractable.

In the majority of patients, cancer pain can be relieved with analgesics:

- **by mouth**: if possible analgesics should be given by mouth. Rectal suppositories are useful in patients with dysphagia, uncontrolled vomiting or gastrointestinal obstruction. Continuous subcutaneous infusion offers an alternative route.

- **by the clock**: analgesics are more effective in preventing pain than in the relief of established pain, therefore doses should be given at fixed time intervals and titrated against the patient’s pain; if pain occurs between doses, a rescue dose should be given, and the next dose increased.

- **by the ladder**: the first step is to give a non-opioid analgesic such as acetylsalicylic acid, paracetamol or ibuprofen, if necessary with an

adjuvant drug. If this does not relieve the pain, an opioid for mild to moderate pain such as codeine should be added. When this combination fails to relieve pain, an opioid for moderate to severe pain such as morphine should be substituted.

- **for the individual**: there are no standard doses for opioid drugs. The range for oral morphine is from as little as 5 mg to more than 100 mg every 4 hours.
- **with attention to detail**: the first and last doses of the day should be linked to the patient’s waking time and bedtime. Ideally the drug regimen should be written out in full for the patient and his or her family. The patient should be warned about possible adverse effects.

### Drugs for neuropathic pain

Neuropathic pain often responds to a tricyclic antidepressant, such as amitriptyline (section 24.2), or to an anticonvulsant such as carbamazepine or sodium valproate (both section 5.1); ketamine (section 1.1.1) or lidocaine (section 12.2) by intravenous infusion may be useful in some situations. Neuropathic pain responds only partially to opioids, but they may be considered when other options fail. A corticosteroid may be required, particularly to relieve pressure and therefore pain in patients with nerve compression.
SECTION 9: ANTIPARKINSON DRUGS

9.1 Drugs used in Parkinsonism
9.2 Drugs used in essential tremor and related disorder
9.1 Drugs used in Parkinsonism

The use of pharmacotherapy will depend upon the degree of incapacity of the patient and is generally not justified until symptoms compromise working ability and social relationships; although levodopa is used in the early stages in some patients. Close supervision is then needed to ensure that treatment regimens are tolerated and that appropriate changes are made to the regimen as the disease progresses.

The most effective form of therapy is a combination of levodopa and a peripheral dopa-decarboxylase inhibitor, such as carbidopa. The response to levodopa with carbidopa is a compromise between increased mobility and adverse effects. Dyskinesias may be dose limiting and increasingly frequent with increased duration of treatment. Many factors including tolerance and progression of the disease may result in complications after 2–5 years of treatment. 'End-of-dose' deterioration occurs when there is a reduced duration of benefit from a dose, resulting in disability and dystonias. The 'on-off' phenomenon is characterized by sudden swings from mobility to episodes of akinesia, tremor and rigidity lasting from a few minutes to several hours. Amelioration of these effects can sometimes be achieved by administering levodopa in a sustained-release preparation or in a greater number of fractionated doses throughout the day. Psychiatric symptoms inducing disruption of sleep, vivid dreams and hallucinations are characteristic adverse effects that may occur at any time, especially in the elderly, and may require dose reduction or withdrawal of levodopa.

Treatment for idiopathic Parkinsonism is often initiated with a dopamine receptor agonist such as bromocriptine. Anticholinergic (more correctly termed antimuscarinic) drugs such as biperiden are usually sufficient in drug-induced Parkinsonism. Antimuscarinic drugs exert their antiparkinsonism by correcting the relative central cholinergic excess thought to occur in Parkinsonism as a result of dopamine deficiency. They reduce tremor and rigidity. They are useful in reducing sialorrhoea.

**LEVODOPA WITH CARBIDOPA**

*Tablets*, levodopa 100 mg with carbidopa 10 mg, levodopa 250 mg with carbidopa 25 mg

**Uses:**
All forms of Parkinsonism other than drug-induced

**Precautions:** Pulmonary disease, peptic ulceration, cardiovascular disease (including previous myocardial infarction); diabetes mellitus, osteomalacia, open-angle glaucoma, history of melanoma (risk of activation), psychiatric illness (avoid if
severe); close monitoring of hepatic, haematological, psychiatric, cardiovascular, and renal function required in long-term therapy; elderly: avoid rapid dose increases; warn patients to resume normal activities gradually; avoid abrupt withdrawal; pregnancy (toxicity in animals) (Appendix 2), breastfeeding (Appendix 3); interactions: Appendix 1

Contraindications:
Concurrent use of monoamine oxidase inhibitors; angle-closure glaucoma; confirmed or suspected malignant melanoma

Dosage:
Parkinsonism, by mouth, ADULT expressed in terms of levodopa, initially 100 mg (with carbidopa 10 mg) twice daily, increased by 100 mg (with carbidopa 10 mg) every few days as necessary, to a maximum of levodopa 1.5 g

ADMINISTRATION.
Optimum daily dose must be determined for each patient by careful monitoring and be taken after meals

Adverse effects:
Nausea, anorexia and vomiting, particularly at the start of treatment; postural hypotension at the start of treatment, particularly in elderly and those receiving antihypertensives; excessive drowsiness and sudden onset of sleep (warn patient of these effects); confusion, vivid dreams, dizziness, tachycardia, arrhythmias; reddish discoloration of body fluids; insomnia, headache, flushing, gastrointestinal bleeding, peripheral neuropathy; taste disturbances, pruritis, rash, liver enzyme changes; psychiatric symptoms including psychosis, depression, hallucinations, delusions and neurological disturbances including dyskinesias may be dose-limiting; painful dystonic spasms (‘end-of-dose’ effects) and (‘on-off’ effects) after prolonged treatment (see notes above); neuroleptic malignant syndrome, on sudden withdrawal; rarely hypersensitivity

BIPERIDEN

Tablets, biperiden hydrochloride 2 mg, 4mg
Injection (Solution for injection), biperiden lactate 5 mg/ml, 1-ml ampoule

Uses:
Drug-induced extrapyramidal symptoms (but not tardive dyskinesias) and adjunctive treatment of Parkinsonism

Contraindications:
Angle-closure glaucoma; untreated urinary retention; prostatic hypertrophy; myasthenia gravis; gastrointestinal obstruction

Precautions:
Elderly; cardiovascular disease, hepatic or renal impairment; avoid abrupt withdrawal; pregnancy and breastfeeding; interactions: Appendix 1

Patient Advice
May impair ability to perform skilled tasks, for example operating machinery, driving

Drug-induced extrapyramidal symptoms, parkinsonism, by mouth, ADULT, as biperiden hydrochloride, initially 1 mg twice daily, increased gradually to 2 mg 3 times daily; usual maintenance dose 3−12 mg daily in divided doses
Drug-induced extrapyramidal symptoms, parkinsonism, by intramuscular injection or slow intravenous injection, Adult, as biperiden lactate, 2.5−5 mg repeated as necessary to maximum 20 mg in 24 hours

**Adverse effects:**
Drowsiness, dry mouth, constipation, blurred vision; hesitancy of micturition, dizziness, tachycardia, arrhythmias; confusion, excitement, agitation, hallucinations, and psychiatric disturbances with high dosage, especially in the elderly and other susceptible patients, may require withdrawal of treatment; impaired memory

**PROCYCLIDINE**

*Injection:* 5 mg/ml; 2ml
*Tablets:* 5mg

**Use**
Adjunct treatment of Parkinson’s disease; treatment of drug induced extrapyramidal symptoms

**Precautions**
Elderly patients require strict dosage regulation. Use with caution in patients with tachycardia, cardiac arrhythmias, hypertension; hypotension, prostatic hyperplasia; liver and kidney disorders; obstructive genito-urinary and gastro-intestinal tracts

**Contraindication**
Narrow-angle glaucoma; pyloric, duodenal obstruction; stenosing peptic ulcer; bladder neck obstruction; myasthenia gravis; achalasia

**Dosage**
ADULTS: 2.5 mg 3 times a day after meals, if tolerated gradual increase dose, max 20mg/day.

**Patient information:**
should be taken with meals

**Adverse effects:**
Drowsiness, dry mouth, constipation, blurred vision; hesitancy of micturition, dizziness, tachycardia, arrhythmias; confusion, excitement, agitation, hallucinations, and psychiatric disturbances with high dosage, especially in the elderly and other susceptible patients, may require withdrawal of treatment; impaired memory
Extrapyrimidal effects (pseudoparkinsonism, akathisia, dystonias, and tardive dyskinesia

Neuroleptic malignant syndrome, impaired temperature regulation, discoloration of skin (blue-gray); hypoglycemia, hyperglycemia, galactorrhea, lactation, breast enlargement, gynecomastia, menstrual irregularities

**BENZHEXOL**

*Tablets: 2mg, 5 mg*

**Use**

Adjunct treatment of Parkinson’s disease; treatment of drug induced extrapyramidal symptoms

**Precautions**

Elderly patients require strict dosage regulation. Use in caution in patients with tachycardia, cardiac arrhythmias, hypertension; hypotension, prostatic hyperplasia; liver and kidney disorders; obstructive genitor-urinary and gastro-intestinal tracts

**Contraindication**

Narrow-angle glaucoma; pyloric, duodenal obstruction; stenosing peptic ulcer; bladder neck obstruction; myasthenia gravis; aschalias

**Dosage**

1 mg daily; increased gradually; usual maintenance dose 5-15mg daily in 3-4 divided dose (max 20 mg daily)

**Adverse effects**

Dry mouth, gastro-intestinal disturbances, dizziness, blurred vision, tachycardia, urinary retension, increase intraocular pressure, nervousness, confusion, excitement, agitation, insomnia
Section 10: Drugs affecting the blood

10.1 Antianaemia medicines
10.2 Medicines affecting coagulation
10.1 Antianaemia drugs

IRON-DEFICIENCY ANAEMIA

Anaemia has many different aetiologies. It occurs when the haemoglobin concentration falls below the normal range for the age and sex of the individual. It is essential that a correct diagnosis is made before initiating therapy. Any serious underlying cause of iron-deficiency anaemia, including gastric erosion and colonic carcinoma, should be excluded before giving iron replacement. Prophylaxis with iron salts in pregnancy should be given to women who have additional factors for iron-deficiency; low-dose iron and folic acid preparations are used for the prophylaxis of megaloblastic anaemia in pregnancy. Ferrous salts should be given orally wherever possible. They differ only marginally in efficiency of absorption and thus the choice of preparation is usually decided by incidence of adverse effects and cost. Ferric salts are much less well absorbed. The oral dose of elemental iron for treatment of iron-deficiency anaemia in adults should be 100–200 mg daily with meals. The approximate elemental iron content of various ferrous salts is ferrous fumarate 200 mg (65 mg iron), ferrous gluconate 300 mg (35 mg iron), ferrous succinate 100 mg (35 mg iron), ferrous sulfate 300 mg (60 mg iron), and dried ferrous sulfate 200 mg (65 mg iron). The haemoglobin concentration should rise by about 100–200 mg/100 ml per day or 2 g/100 ml over 3–4 weeks. After the haemoglobin has risen to normal, treatment should be continued for a further 3 months to replenish the iron stores. Iron intake in the evening has been reported to improve its absorption. Iron intake with meals may reduce bioavailability but improve tolerability and adherence. If adverse effects arise with one salt, dosage can be reduced or a change made to an alternative iron salt but an improvement in tolerance may be due to lower content of elemental iron. Gastrointestinal irritation may occur with iron salts. Nausea and epigastric pain are dose-related. Iron preparations taken orally may be constipating, particularly in the elderly, occasionally leading to faecal impaction. Oral iron may exacerbate diarrhoea in patients with inflammatory bowel disease but care is also needed in patients with intestinal strictures and diverticula. Iron as iron dextran (a complex of ferric hydroxide with dextrans) should be given parenterally only if the patient cannot tolerate oral iron, or does not take it reliably or there is continuing severe blood loss or malabsorption. Many patients with chronic renal failure who are receiving haemodialysis (and some on peritoneal dialysis) require intravenous iron on a regular basis. Parenteral iron may cause more harm than benefit. With the exception of patients on haemodialysis the haemoglobin
response is not significantly faster with the parenteral route than the oral route.

MEGALOBLASTIC ANAEMIAS

Megaloblastic anaemias result from a lack of either vitamin B_{12} (hydroxocobalamin) or folic acid or both. The clinical features of folate-deficient megaloblastic anaemia are similar to those of vitamin B_{12} deficiency except that the accompanying severe neuropathy does not occur; it is essential to establish the underlying cause in every case. Hydroxocobalamin is used to treat vitamin B_{12} deficiency whether due to dietary deficiency or malabsorption including pernicious anaemia (due to a lack of intrinsic factor, which is essential for vitamin B_{12} absorption). Folate deficiency due to poor nutrition, pregnancy, antiepileptics or malabsorption is treated with folic acid but this should never be administered without vitamin B_{12} in undiagnosed megaloblastic anaemia because of the risk of precipitating neurological changes due to vitamin B_{12} deficiency.

Preparations containing a ferrous salt and folic acid are used for the prevention of megaloblastic anaemia in pregnancy. The low doses of folic acid in these preparations are inadequate for the treatment of megaloblastic anaemias.

PREVENTION OF NEURAL TUBE DEFECTS

An adequate intake of folic acid before conception and during early pregnancy reduces the risk of neural tube defects in babies. Therefore, women planning a pregnancy should receive sufficient folic acid before conception and in the first 12 weeks of pregnancy; folic acid may be given as a food or a medicinal supplement in a dose of 400–500 micrograms daily. A woman who has not received supplementary folic acid and suspects that she might be pregnant should start taking folic acid at once and continue until week 12 of pregnancy.

Women at increased risk of giving birth to a baby with neural tube defects (for example history of neural tube defect in a previous child) should receive a higher dose of folic acid of approximately 5 mg daily, starting before conception and continuing for 12 weeks after conception. Women taking antiepileptic medication should be counselled by their doctor before starting folic acid.

FERROUS SALTS

Tablets, dried ferrous sulfate 200 mg (65 mg iron); ferrous sulfate 300 mg (60 mg iron); ferrous fumarate 210 mg (68 mg iron); ferrous gluconate 300 mg (35 mg iron)

Oral solution, ferrous sulfate (25 mg iron)/mL

Uses:  
iron-deficiency anaemia

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; pregnancy; peptic ulcer, regional enteritis, ulcerative colitis, intestinal strictures, diverticula; **overdosage:** see section 4.2.4; **interactions:** Appendix 1

Dosage:  
Iron-deficiency anaemia, by mouth, ADULT elemental iron 100–200 mg daily in divided doses  
Prevention of iron deficiency anaemia (in those at particular risk), by mouth, adult (woman) elemental iron 60 mg daily; child under 5 years elemental iron 2 mg/kg (maximum 30 mg) daily, over 5 years elemental iron 30 mg daily; in women and children over 5 years, folic acid may also be given

Patient Advice.  
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 (and if possible swallowed through a drinking straw to prevent discolouration of the teeth)

Adverse effects:  
constipation, diarrhoea, dark stools, nausea, epigastric pain, gastrointestinal irritation; long-term or excessive administration may cause haemosiderosis

**FOLIC ACID**

**Tablets**, folic acid 1 mg, 5 mg

Uses:  
treatment of folate-deficiency megaloblastic anaemia; prevention of neural tube defect in pregnancy (see notes above)

Contraindications:  
should never be given without vitamin B₁₂ in undiagnosed megaloblastic anaemia or other vitamin B₁₂ deficiency states because risk of precipitating subacute combined degeneration of the spinal cord; folate-dependent malignant disease

Precautions:  
women receiving antiepileptic therapy need counselling before starting folic acid; **interactions:** Appendix 1

Dosage:  
Treatment of folate-deficiency, megaloblastic anaemia, by mouth, ADULT 5 mg daily for 4 months; up to 15 mg daily may be necessary in malabsorption states

Prevention of first occurrence of neural tube defect, by mouth, ADULT 400–500 micrograms daily before conception and during the first twelve weeks of pregnancy
Prevention of recurrence of neural tube defect, by mouth, ADULT 5 mg daily (reduced to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until twelfth week of pregnancy

FERROUS SALT WITH FOLIC ACID

Tablets, dried ferrous sulfate 325 mg (105 mg iron), folic acid 350 micrograms; dried ferrous sulfate 160 mg (50 mg iron), folic acid 400 micrograms; ferrous fumarate 322 mg (105 mg iron), folic acid 350 micrograms

Uses:
prevention of iron and folic acid deficiencies in pregnancy

Precautions:
low doses of folic acid in the combination preparations above are inadequate for treatment of megaloblastic anaemia; over-dosage: see section 4.2.4; interactions: Appendix 1

Dosage:
Severe anaemia, by mouth, adult elemental iron 120 mg daily with folic acid 400 micrograms daily for 3 months; child under 2 years elemental iron 25 mg daily with folic acid 100–400 micrograms daily for 3 months, 2–12 years elemental iron 60 mg daily with folic acid 400 micrograms daily for 3 months

Prevention of iron and folic acid deficiencies in pregnancy, by mouth ADULT the equivalent of about 100 mg elemental iron with 350–400 micrograms folic acid daily throughout pregnancy

Adverse effects:
see Ferrous salts

HYDROXOCOBALAMIN

Injection (Solution for injection), hydroxocobalamin 1 mg/ml, 1-ml ampoule

Uses:
megaloblastic anaemia due to vitamin B₁₂ deficiency

Precautions:
except in emergencies, should not be given before diagnosis confirmed; monitor serum potassium levels—arrhythmias secondary to hypokalaemia in early therapy

Dosage:
Megaloblastic anaemia without neurological involvement, by intramuscular injection, ADULT and CHILD initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months
Megaloblastic anaemia with neurological involvement, by *intramuscular injection*, **ADULT** and **CHILD** initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months

Prophylaxis of macrocytic anaemias, *by intramuscular injection*, **ADULT** and **CHILD** 1 mg every 2–3 months

Tobacco amblyopia and Leber optic atrophy, *by intramuscular injection*, **ADULT** and **CHILD** 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months

**Adverse effects:** itching, exanthema, fever, chills, hot flushes, nausea, dizziness; rarely acneiform and bullous eruptions, anaphylaxis

### 10.2 Drugs affecting coagulation

Anticoagulants are used to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. They are therefore used widely in the prevention and treatment of deep-vein thrombosis in the legs, prophylaxis of embolization in rheumatic heart disease and atrial fibrillation and to prevent thrombi forming on prosthetic heart valves.

**Heparin** is a parenteral anticoagulant that initiates anticoagulation rapidly but has a short duration of action. The low molecular weight heparins have a longer duration of action.

For the treatment of deep venous thrombosis and pulmonary embolism heparin is given as an intravenous loading dose followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection. An oral anticoagulant is started at the same time as heparin. The heparin needs to be continued for at least 5 days, until the oral anticoagulant has taken effect and the INR (international normalized ratio) has been in the therapeutic range for 2 consecutive days. Laboratory monitoring is essential, on a daily basis. Heparin is also used in regimens for the management of myocardial infarction, the management of unstable angina, acute peripheral arterial occlusion and in dialysis.

In patients undergoing general surgery, low-dose heparin by subcutaneous injection is used to prevent postoperative deep-vein thrombosis and pulmonary embolism in high risk patients (those with obesity, malignant disease, history of deep-vein thrombosis or pulmonary embolism, patients over 40 years, those with an established thrombophilic disorder or those undergoing major or complicated surgery). It is also of value in high-risk medical patients, for example obesity, heart failure, when confined to bed.
If haemorrhage occurs it is usually sufficient to withdraw heparin, but if rapid reversal of the effects of heparin is required, **protamine sulfate** is a specific antidote. Oral anticoagulants take at least 48–72 hours for the anticoagulant effect to develop fully; if an immediate effect is needed, heparin must be given concomitantly. **Warfarin** is indicated in deep-vein thrombosis, pulmonary embolism, for patients with atrial fibrillation who are at risk of embolization and for those with mechanical prosthetic heart valves (to prevent emboli developing on the valves); oral anticoagulants should not be used in cerebral thrombosis or peripheral arterial occlusion as first-line therapy. The main adverse effect of oral anticoagulants is haemorrhage. Prothrombin time (usually reported as INR, international normalized ratio) should be checked on a daily basis initially then at longer intervals depending on response. If severe haemorrhage occurs, stop warfarin and give **phytomenadione** (vitamin K) by slow intravenous injection.

**ANTICOAGULANTS IN PREGNANCY**

Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Women at risk of pregnancy should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality. Oral anticoagulants cross the placenta with the risk of placental or fetal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, oral anticoagulants should be avoided in pregnancy, especially in the first and third trimester. Difficult decisions may have to be made, particularly in women with prosthetic heart valves or with a history of recurrent venous thrombosis or pulmonary embolism.

**HAEMOPHILIA**

Desmopressin [not included on WHO Model List] by injection may aid haemostasis and be useful in mild forms of haemophilia. For minor procedures including dental surgery, it may circumvent the need for factor VIII. For the use of factor VIII and factor IX in haemophilia, see section 11.2.

**HEPARIN SODIUM**

*Injection* (Solution for injection), heparin sodium 1000 units/ml, 1-ml ampoule; 5000 units/ml, 1-ml ampoule; 25 000 units/ml, 1-ml ampoule

**Uses:**
treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism

**Contraindications:**
hypersensitivity to heparin; haemophilia and other haemor-
rhagic 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)

Precautions:
hepatic impairment (Appendix 5) and renal failure (Appendix 4); hypersensitivity to low molecular weight heparins; spinal or epidural anaesthesia—risk of spinal haematoma; pregnancy (Appendix 2); diabetes mellitus, acidosis, concomitant potassium-sparing drugs—increased risk of hyperkalaemia; interactions: Appendix 1

Dosage:
Treatment of deep-vein thrombosis and pulmonary embolism: by intravenous injection, ADULT loading dose of 5000 units (10 000 units in severe pulmonary embolism) followed by continuous intravenous infusion of 15–25 units/kg/hour or by subcutaneous injection of 15 000 units every 12 hours; laboratory monitoring is essential, preferably on a daily basis and dose adjusted accordingly; by intravenous injection, SMALL ADULT and CHILD, lower loading dose, then by continuous intravenous infusion, 15–25 units/kg/hour or by subcutaneous injection, 250 units/kg every 12 hours

Prophylaxis in general surgery, by subcutaneous injection, ADULT 5000 units 2 hours before surgery, then every 8–12 hours for 7 days or until patient is ambulant (monitoring not needed); during pregnancy (with monitoring) 5000–10 000 units every 12 hours (important: not intended to cover prosthetic heart valve management in pregnancy, which requires specialist management)

Adverse effects:
immune-mediated thrombocytopenia usually developing 6 to 10 days after commencement of therapy (requires immediate withdrawal of heparin); haemorrhage, skin necrosis, hypersensitivity reactions including urticaria, angioedema and anaphylaxis; osteoporosis after prolonged use and rarely alopecia

WARFARIN SODIUM

Warfarin is a representative oral anticoagulant. Various drugs can serve as alternatives

Tablets, warfarin sodium 1 mg, 2 mg, 5 mg

Uses:
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 (see notes above and Appendix 2); peptic ulcer, severe hypertension, bacterial endocarditis

Precautions:
hepatic impairment (Appendix 5) or renal failure (Appendix 4), recent surgery, breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:

NOTE. Wherever possible, the base-line prothrombin time should be determined before the initial dose is given

Prophylaxis and treatment of thromboembolic disorders, by mouth, ADULT usual induction dose is 10 mg daily for 2 days, according to the individual patient; the subsequent dose depends upon the prothrombin time; the usual daily maintenance dose is 3–9 mg taken at the same time each day

Adverse effects:
haemorrhage; hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haematocrit, ‘purple toes’, skin necrosis, jaundice, hepatic dysfunction, nausea, vomiting and pancreatitis

Reversal of anticoagulation

PROTAMINE SULFATE

Injection (Solution for injection), protamine sulfate 10 mg/ml, 5-ml ampoule

Uses:
antidote to overdosage with heparin

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, men who are infertile or who have had a vasectomy

Dosage:
Heparin overdose, by intravenous injection over approximately 10 minutes, 1 mg neutralizes 80–100 units heparin when given within 15 minutes; if longer time, less protamine needed as heparin is rapidly excreted

Adverse effects:
nausea, vomiting, lassitude, flushing, hypotension, brady-cardia, dyspnoea, allergic reactions (including angioedema, anaphylaxis)

Phytomenadione

Tablets, phytomenadione 10 mg
Injection (Solution for injection), phytomenadione 10 mg/ml, 5-ml ampoule

Uses:
antagonist to warfarin; prophylaxis against haemorrhagic disease of the newborn

Precautions:
reduce dose in elderly; hepatic impairment; not an antidote to heparin; pregnancy (Appendix 2);

interactions: Appendix 1

Dosage:
Warfarin-induced hypoprothrombinaemia; no bleeding or minor bleeding, by slow intravenous injection, ADULT 500 micrograms or by mouth, ADULT 5 mg; less severe haemorrhage, by mouth or by intramuscular injection, ADULT 10–20 mg; severe haemorrhage, ADULT, by slow intravenous injection, 2.5–5 mg; very rarely up to 50 mg (but risk of overcorrection with high dosage)

Haemorrhagic disease of the newborn, treatment, by intravenous or intramuscular injection, NEONATE 1 mg with further doses if necessary at 8-hour intervals

Haemorrhagic disease of the newborn, prophylaxis, by intramuscular injection, NEONATE 0.5–1 mg as single dose or by mouth, 2 mg followed by a second dose after 4–7 days and for breastfed babies a third dose after 1 month

Adverse effects:
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
SECTION 11:
BLOOD PRODUCTS AND PLASMA SUBSTITUTES

11.1 Plasma substitute
11.2 Plasma Fraction for specific use
Blood products and plasma substitutes

11.1 Plasma substitutes

**Albumin** solution, prepared from whole blood, contains soluble protein and electrolytes but no clotting factors, blood group antibodies; they may be given without regard of patient blood type. **Albumin** solution is used for the treatment of severe hypo-proteinaemia, particularly when associated with a low plasma volume. Concentrated albumin solution.

**Dextran 70** is a macromolecular substance which is metabolized slowly; they may be used to expand and maintain blood volume in shock arising from conditions such as burns or septicæmia. They are rarely needed when shock is due to sodium and water depletion as, in these circumstances, the shock responds to water and electrolyte repletion.

Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water and electrolytes over periods of several days. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Plasma substitutes may be used as an immediate short-term measure to treat massive haemorrhage until blood is available, but large volumes of some plasma substitutes can increase the risk of bleeding by depleting coagulation factors. Dextran may interfere with blood group cross-matching or biochemical measurements and these should be carried out before the infusion is started.

**Albumin Solution**

(Human albumin solution- Plasma Protein Fraction Human)
A solution containing protein derived from plasma, serum, or placenta; at least 95% of the protein is albumin

**Use**
Plasma volume expansion and maintenance of cardiac output in the treatment of certain types of shock or impending shock; may be useful in burnt patients, ARDS, and cardiopulmonary bypass;

**Precaution**
Use with caution in patients with hepatic or renal failure because of added protein load; rapid infusion of albumin may cause vascular overload. Avoid 25% concentration in preterm infants due to risk of intraventricular hemorrhage. History of cardiac or circulatory disease (administer slowly)

**Contraindicated**
Cardiac failure; severe anemia

**Adverse effects**
Hypersensitivity reactions (including anaphylaxis) with vomiting, nausea, increase salivation, fever tachycardia, hypotension and chills.

**Dosage**
- **I.V**: 5% should be used in hypovolemic patients or intravascularly-depleted patients
- 25% should be used in patients whom fluids and sodium intake must be minimized

**Children**:
- Emergency initial dose: 25g
- Nonemergencies: 25%-50% of the adult dose

**ADULTS**: usual dose 25g; initial dose may be repeated every 15-30 minutes if no response is adequate; no more than 250g should be administered within 48 hours

**Hypoproteinemia**: 0.5-1g/kg/dose; repeat every 1-2 days

**Hypovolemia**: 0.5-1g/kg/dose; repeat as needed; maximum dose 6g/kg/day

**Administration**: For I.V. administration only, use within 4 hours after opening vial, discard unused portion

- 5%: Do not exceed 2-4 ml/minute in patients with normal plasma volume: 5-10ml/minute in patients with hypoproteinemia.
- 25%: Do not exceed 1ml/minute in patients with normal plasma volume; 2-3ml/minute in patients with hypoproteinemia.

**DEXTRAN 70**

*Infusion* (Solution for infusion), dextran 70 6% in glucose intravenous infusion 5% or sodium chloride intravenous infusion 0.9%

**Uses**:
- Short-term blood volume expansion

**Contraindications**:
- Severe congestive heart failure, renal failure; bleeding disorders such as thrombocytopenia and hypofibrinogenemia

**Precautions**:
- Cardiac disease or renal impairment; monitor urine output; avoid haematocrit falling below 25–30%; where possible, monitor central venous pressure; can interfere with blood group cross-matching and biochemical tests—take samples before start of infusion; monitor for hypersensitivity reactions; pregnancy (Appendix 2)

**Dosage**:
- Short-term blood volume expansion, *by rapid intravenous infusion*, adult 500–1000 ml initially, followed by 500 ml if necessary; total dosage should not exceed 20 ml/kg during the initial 24 hours; if required 10 ml/kg daily may be given for a further 2 days (treatment should not continue for longer than 3 days);
- child total dosage should not exceed 20 ml/kg

**Adverse effects**:
Hypersensitivity reactions including fever, nasal congestion, joint pains, urticaria, hypotension, bronchospasm—rarely severe anaphylactoid reactions; transient increase in bleeding time

11.2 Plasma fractions for specific use

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. Deficiency in any of these factors results in haemophilia. Bleeding episodes in haemophilia require prompt treatment with replacement therapy. **Factor VIII**, used for the treatment of haemophilia A, is a sterile freeze-dried powder containing the blood coagulation factor VIII fraction prepared from pooled human venous plasma. Standard factor VIII preparations also contain von Willebrand factor and may be used to treat von Willebrand disease. Highly purified preparations, including recombinant factor VIII, are available; they are indicated for the treatment of haemophilia A but do not contain sufficient von Willebrand factor for use in the management of von Willebrand disease. **Factor IX Complex** is a sterile freeze-dried concentrate of blood coagulation factors II, VII, IX and X derived from fresh venous plasma. Factor IX complex which is used for the treatment of haemophilia B may also be used for the treatment of bleeding due to deficiencies of factor II, VII, and X. High purity preparations of factor IX which do not contain clinically effective amounts of factor II, VII, and X are available. A recombinant factor IX preparation is also available.

**Factor VIII concentrate**


Factor VIII concentrate is a complementary preparation and a representative coagulation factor preparation. Various preparations can serve as alternatives

**Infusion** (Powder for solution for infusion), factor VIII 250–1500 units

**Uses:**
Control of haemorrhage in haemophilia A

**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)
Dosage:
Haemophilia A, by slow intravenous infusion, ADULT and CHILD according to patient’s needs
Adverse effects:
Allergic reactions including chills, fever

Factor IX complex (coagulation factors II, VII, IX, X) concentrate

Factor IX complex concentrate is a complementary preparation and a representative coagulation factor preparation. Various preparations can serve as alternatives
Infusion (Powder for solution for infusion), factor II, VII, IX, and X 500–1500 units
Uses:
Replacement therapy for factor IX deficiency in haemophilia; bleeding due to deficiencies of factors II, VII or X
Contraindications:
Disseminated intravascular coagulation
Precautions:
Risk of thrombosis (probably less risk with highly purified preparations)
Dosage:
Haemophilia B, by slow intravenous infusion, ADULT and CHILD according to patient’s needs and specific preparation used
Treatment of bleeding due to deficiencies in factor II, VII or X as well as IX, by slow intravenous infusion, ADULT and CHILD according to patient’s needs
Adverse effects:
Allergic reactions including chills, fever
Section 12: Cardiovascular drugs

12.1 Antianginal medicines
12.2 Antiarrhythmic medicines
12.3 Antihypertensive medicines
12.4 Medicines used in heart failure
12.5 Antithrombotic drugs and myocardial infarction
12.6 Lipid-regulation drugs
Cardiovascular drugs

12.1 Antianginal drugs

The three main types of angina are:

- **stable angina** (angina of effort), where atherosclerosis restricts blood flow in the coronary vessels; attacks are usually caused by exertion and relieved by rest
- **unstable angina** (acute coronary insufficiency), which is considered to be an intermediate stage between stable angina and myocardial infarction
- **Prinzmetal angina** (variant angina), caused by coronary vasospasm, in which attacks occur at rest.

Management depends on the type of angina and may include drug treatment, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

**Stable angina**

Drugs are used both for the relief of acute pain and for prophylaxis to reduce further attacks; they include organic nitrates, beta-adrenoceptor antagonists (beta-blockers), and calcium-channel blockers.

**NITRATES**

Organic nitrates have a vasodilating effect; they are sometimes used alone, especially in elderly patients with infrequent symptoms. Tolerance leading to reduced antianginal effect is often seen in patients taking prolonged-action nitrate formulations. Evidence suggests that patients should have a 'nitrate-free' interval to prevent the development of tolerance. Adverse effects such as flushing, headache, and postural hypotension may limit nitrate therapy but tolerance to these effects also soon develops. The short-acting sublingual formulation of glyceryl trinitrate is used both for prevention of angina before exercise or other stress and for rapid treatment of chest pain. A sublingual tablet of isosorbide dinitrate is more stable in storage than glyceryl trinitrate and is useful in patients who require nitrates infrequently; it has a slower onset of action, but effects persist for several hours.

**BETA-BLOCKERS**

Beta-adrenoceptor antagonists (beta-blockers), such as atenolol, block beta-adrenergic receptors in the heart, and thereby decrease heart rate and myocardial contractility and oxygen consumption, particularly during exercise. Beta-blockers are first-line therapy for patients with effort-induced chronic stable angina; they improve exercise tolerance, relieve symptoms, reduce the severity and frequency of angina attacks,
and increase the anginal threshold. Beta-blockers should be withdrawn gradually to avoid precipitating an anginal attack; they should not be used in patients with underlying coronary vasospasm (Prinzmetal angina). Beta-blockers may precipitate asthma and should not be used in patients with asthma or a history of obstructive airways disease. Some, including atenolol, have less effect on beta2 (bronchial) receptors and are therefore relatively cardioselective. Although they have less effect on airways resistance they are not free of this effect and should be avoided. Beta-blockers slow the heart and may induce myocardial depression, rarely precipitating heart failure. They should not be given to patients who have incipient ventricular failure, second- or third-degree atrioventricular block, or peripheral vascular disease. Beta-blockers should be used with caution in diabetes since they may mask the symptoms of hypoglycaemia, such as rapid heart rate. Beta-blockers enhance the hypoglycaemic effect of insulin and may precipitate hypoglycaemia.

**CALCIUM-CHANNEL BLOCKERS**

A calcium-channel blocker, such as verapamil, is used as an alternative to a beta-blocker to treat stable angina. Calcium-channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle. Myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed and coronary or systemic vascular tone may be diminished. Calcium-channel blockers are used to improve exercise tolerance in patients with chronic stable angina due to coronary atherosclerosis or with abnormally small coronary arteries and limited vasodilator reserve. Calcium-channel blockers can also be used in patients with unstable angina with a vasospastic origin, such as Prinzmetal angina, and in patients in whom alterations in cardiac tone may influence the angina threshold. Diltiazem is effective in most forms of angina; the longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers.

**Unstable angina**

Unstable angina requires prompt aggressive treatment to prevent progression to myocardial infarction. Initial treatment is with acetylsalicylic acid to inhibit platelet aggregation, followed by heparin. Nitrates and beta-blockers
are given to relieve ischaemia; if beta-blockers are contraindicated, verapamil is an alternative, provided left ventricular function is adequate.

**Prinzmetal angina**
Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

**Atenolol**

*Tablets*, atenolol 50 mg, 100 mg

*Injection* (Solution for injection), atenolol 500 micrograms/ml, 10-ml ampoule

**Uses:**
Angina and myocardial infarction; arrhythmias (section 12.2); hypertension (section 12.3); migraine prophylaxis (section 7.2)

**Contraindications:**
Asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker)

**Precautions:**
avoid abrupt withdrawal in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment (Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); myasthenia gravis;

**Interactions:** Appendix 1

**Dosage:**
Angina, *by mouth*, ADULT 50 mg once daily, increased if necessary to 50 mg twice daily or 100 mg once daily

Myocardial infarction (early intervention within 12 hours), *by intravenous injection* over 5 minutes, ADULT 5 mg, then *by mouth* 50 mg after 15 minutes, followed by 50 mg after 12 hours, then 100 mg daily

**Adverse effects:**
Gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyper-
glycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

GLYCERYL TRINITRATE

Sublingual tablets, glyceryl trinitrate 500 micrograms

Note.
Glyceryl trinitrate tablets are unstable. They should therefore be dispensed in glass or stainless steel containers, and closed with a foil-lined cap which contains no wadding. No more than 100 tablets should be dispensed at one time, and any unused tablets should be discarded 8 weeks after opening the container

Uses:
Prophylaxis and treatment of angina

Contraindications:
hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma

Precautions:
Severe hepatic or renal impairment; hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction;

interactions: Appendix 1

Dosage:
Angina, sublingually, ADULT 0.5–1 mg, repeated as required

Adverse effects:
Throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported)

ISOSORBIDE DINITRATE

Isosorbide dinitrate is a representative nitrate vasodilator. Various drugs can serve as alternatives

Sublingual tablets, isosorbide dinitrate 10 mg

Uses:
Prophylaxis and treatment of angina; heart failure (section 12.4)

Contraindications:
Hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma

Precautions:
Severe hepatic or renal impairment; hypothyroidism; malnu-
trition; hypothermia; recent history of myocardial infarction; interactions: Appendix 1

Dosage:
Angina, sublingually, ADULT 0.5–1 mg, repeated as required

Adverse effects:
Throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported)

**ISOSORBIDE DINITRATE**

Isosorbide dinitrate is a representative nitrate vasodilator. Various drugs can serve as alternatives

*Sublingual tablets*, isosorbide dinitrate 10 mg

Uses:
Prophylaxis and treatment of angina; heart failure (section 12.4)

Contraindications:
Hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma

Precautions:
Severe hepatic or renal impairment; hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; interactions: Appendix 1

Tolerance.
Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the antianginal effect; this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-hour rather than a 12-hour interval, thus ensuring a nitrate-free interval each day

Dosage:
Angina (acute attack), sublingually, ADULT 5–10 mg, repeated as required

Angina prophylaxis, by mouth, ADULT 30–120 mg daily in divided doses (see advice on Tolerance above)

Adverse effects:
Throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported)

**VERAPAMIL HYDROCHLORIDE**

*Tablets*, verapamil hydrochloride 80 mg, 120 mg

*Injection*, 75mg/ml

Uses:
Angina, including stable, unstable, and Prinzmetal; arrhythmias (section 12.2)

Contraindications:
Hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria

Precautions:
first-degree atrioventricular block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment (Appendix 5); children (specialist advice only); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice; interactions: Appendix 1

Dosage:
Angina, by mouth, ADULT 80–120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina)

Adverse effects:
Constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect)

DILTIAZEM HYDROCHLORIDE

Tablets, 60mg

Use
Prophylaxis and treatment of angina; hypertension

Precaution
Reduce dose in hepatic and renal impairment; heart failure or significantly impaired left ventricular function, bradycardia (avoid if severe), first degree AV block, or prolong PR interval,

Contraindications
Severe bradycardia, left ventricular failure, second or third degree AV block (unless pacemaker fitted) sick sinus syndrome; pregnancy and breast feeding

Adverse Reactions
Bradycardia, sino- atrial, AV block, palpitations, dizziness, hypotension, malaise, asthenia, headache, hot flashes, GI disturbances, oedema,

Dosage
Angina, 60mg, 3 times daily (elderly initially twice a day); increase if necessary to 360mg daily.
12.2 Antiarrhythmic drugs

Treatment of arrhythmias requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment. Antiarrhythmic drugs must be used cautiously since most drugs that are effective in treating arrhythmias can provoke them in some circumstances; this arrhythmogenic effect is often enhanced by hypokalaemia. When antiarrhythmic drugs are used in combination, their cumulative negative inotropic effects may be significant, particularly if myocardial function is impaired.

Atrial fibrillation
The increased ventricular rate in atrial fibrillation can be controlled with a beta-adrenoceptor antagonist (beta-blocker) or verapamil. Digoxin is often effective for controlling the rate at rest; it is also appropriate if atrial fibrillation is accompanied by congestive heart failure. Intravenous digoxin is occasionally required if the ventricular rate needs rapid control. If adequate control at rest or during exercise cannot be achieved readily verapamil may be introduced with digoxin, but it should be used with caution if ventricular function is impaired. Anticoagulants are indicated especially in valvular or myocardial disease, and in the elderly. Warfarin is preferred to acetylsalicylic acid in preventing emboli. If atrial fibrillation began within the previous 48 hours and there does not appear to be a danger of thromboembolism, antiarrhythmic drugs, such as procainamide or quinidine, may be used to terminate the fibrillation or to maintain sinus rhythm after cardioversion.

Atrial flutter
Digoxin will sometimes slow the ventricular rate at rest. Reversion to sinus rhythm is best achieved by direct current electrical shock. If the arrhythmia is long-standing, treatment with an anticoagulant should be considered before cardioversion to prevent emboli. Intravenous verapamil reduces ventricular fibrillation during paroxysmal (sudden onset and intermittent) attacks of atrial flutter. An initial intravenous dose may be followed by oral treatment; hypotension may occur with high doses. It should not be used for tachyarrhythmias where the QRS complex is wide unless a supraventricular origin has been established beyond doubt. If the flutter cannot be restored to sinus rhythm, antiarrhythmics such as quinidine can be used.

Paroxysmal supraventricular tachycardia
In most patients this remits spontaneously or can revert to sinus rhythm by reflex vagal stimulation. Failing this, intravenous
injection of a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective. Verapamil and a beta-blocker should \textbf{never} be administered concomitantly because of the risk of hypotension and asystole.

\textbf{Ventricular tachycardia}

Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. In more stable patients intravenous \textit{lidocaine} or \textit{procainamide} may be used. After sinus rhythm is restored, drug therapy to prevent recurrence of ventricular tachycardia should be considered; a beta-adrenoceptor antagonist (beta-blocker) or verapamil may be effective.\textit{Torsades de pointes} is a special form of ventricular tachycardia associated with prolongation of the QT interval. Initial treatment with intravenous infusion of \textit{magnesium sulfate} (usual dose 2 g over 10–15 minutes, repeated once if necessary) together with temporary pacing is usually effective; alternatively, isoprenaline infusion may be given with extreme caution until pacing can be instituted. \textit{Isoprenaline} is an inotropic sympathomimetic; it increases the heart rate and therefore shortens the QT interval, but given alone it may induce arrhythmias. \textit{Disopyramide} Oral administration of disopyramide is useful but it has antimuscarinic effect which limits its use in patients with glaucoma or prostatic hypertrophy.

\textbf{Bradyarrhythmias}

Sinus bradycardia (less than 50 beats/minute) associated with acute myocardial infarction may be treated with atropine. Temporary pacing may be required in unresponsive patients. Drugs are of limited value for increasing the sinus rate long term in the presence of intrinsic sinus node disease and permanent pacing is usually required.

\textbf{Cardiac arrest}

In cardiac arrest, \textit{epinephrine} (adrenaline) is given by intravenous injection in a dose of 1 mg (10 ml of 1 in 10 000 solution) as part of the procedure for cardiopulmonary resuscitation.

\textbf{ATENOLOL}

Atenolol is a representative beta-adrenoceptor antagonist. Various drugs can serve as alternatives \textit{Tablets}, atenolol 50 mg, 100 mg

\textbf{Uses:}

arrhythmias; angina (section 12.1); hypertension (section 12.3); migraine prophylaxis (section 7.2)

\textbf{Contraindications:}

asthma or history of obstructive airways disease (unless no
alternative, then with extreme caution and under specialist supervision); uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker)

**Precautions:**

avoid abrupt withdrawal especially in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment (Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)); myasthenia gravis; **interactions:** Appendix 1

**Dosage:**

Arrhythmias, by mouth, ADULT 50 mg once daily, increased if necessary to 50 mg twice daily or 100 mg once daily

**Adverse effects:**

gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

**DIGOXIN**

*Tablets*, digoxin 125 micrograms, 250 micrograms

*Oral solution*, digoxin 50 micrograms/ml

*Injection* (Solution for injection), digoxin 250 micrograms/ml, 2-ml ampoule

**Uses:**

Supraventricular arrhythmias, particularly atrial fibrillation; heart failure (section 12.4)

**Contraindications:**

Hypertrophic obstructive cardiomyopathy (unless also atrial fibrillation and heart failure); Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation; intermittent complete heart block; second-degree atrioventricular block

**Precautions:**

Recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; elderly (reduce dose); renal impairment (Appendix 4); avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythm-
mias); pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Atrial fibrillation, by mouth, ADULT 1–1.5 mg in divided doses over 24 hours for rapid digitalization or 250 micrograms 1–2 times daily if digitalization less urgent; maintenance 62.5–500 micrograms daily (higher dose may be divided), according to renal function and heart rate response; usual range 125–250 micrograms daily (lower dose more appropriate in elderly)
Emergency control of atrial fibrillation, by intravenous infusion over at least 2 hours, ADULT 0.75–1 mg

Note.
Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks

Adverse effects:
usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported

Epinephrine (adrenaline)

Injection (Solution for injection), epinephrine hydrochloride 100 micrograms/ml (1 in 10 000), 10-ml ampoule

Uses:
Cardiac arrest; anaphylaxis (section 3.1)

Precautions:
Heart disease, hypertension, arrhythmias, cerebrovascular disease; hyperthyroidism, diabetes mellitus; angle-closure glaucoma; second stage of labour; interactions: Appendix 1

Dosage:
Caution: different dilutions of epinephrine injection are used for different routes of administration
Cardiac arrest, by intravenous injection through a central line using epinephrine injection 1 in 10 000 (100 micrograms/ml), ADULT 1 mg (10 ml), repeated at 3-minute intervals if necessary

Note.
If central line not in place, same dose is given via peripheral vein, then flushed through with at least 20 ml sodium chloride 0.9% injection (to expedite entry into circulation)

Adverse effects:
anxiety, tremor, tachycardia, headache, cold extremities; nausea, vomiting, sweating, weakness, dizziness, hyperglycaemia also reported; in overdosage arrhythmias, cerebral haemorrhage, pulmonary oedema
LIDOCAINE HYDROCHLORIDE

Injection (Solution for injection), lidocaine hydrochloride 20 mg/ml, 2-ml ampoule

Uses:
Ventricular arrhythmias (especially after myocardial infarction); local anaesthesia (section 1.2)

Contraindications:
Sino-atrial disorder, any grade of atrioventricular block or any other type of conduction disturbances, severe myocardial depression, acute porphyria or hypovolaemia

Precautions:
Lower dosage in congestive heart failure, bradycardia, hepatic impairment (Appendix 5), marked hypoxia, severe respiratory depression, following cardiac surgery and in elderly; pregnancy (Appendix 2), breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Ventricular arrhythmias, by intravenous injection, ADULT, loading dose of 50–100 mg (or 1–1.5 mg/kg) at a rate of 25–50 mg/minute, followed immediately by intravenous infusion of 1–4 mg/minute, with ECG monitoring of all patients (reduce infusion dose if required for longer than 24 hours)

IMPORTANT.
Following intravenous injection lidocaine has a short duration of action (of 15–20 minutes). If it cannot be given by intravenous infusion immediately, the initial intravenous injection of 50–100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

Adverse effects:
Dizziness, paraesthesia, drowsiness, confusion, apnoea, respiratory depression, coma, seizures, and convulsions, hypotension, arrhythmias, heart block, cardiovascular collapse and bradycardia (may lead to cardiac arrest); nystagmus often an early sign of lidocaine overdosage

QUINIDINE SULFATE

Quinidine is a representative antiarrhythmic drug. Various drugs can serve as alternatives
Quinidine sulfate is also a complementary antiarrhythmic drug for use when drugs in the core list cannot be made available

Tablets, quinidine sulfate 200 mg

Note.
Quinidine sulfate 200 mg = quinidine bisulfate 250 mg

Uses:
suppression of supraventricular arrhythmias and ventricular arrhythmias; maintenance of sinus rhythm after cardioversion

of atrial fibrillation

**Contraindications:**
Complete heart block

**Precautions:**
Partial heart block; extreme care in uncompensated heart failure, myocarditis, severe myocardial damage; myasthenia gravis; acute infections or fever (symptoms may mask hypersensitivity reaction to quinidine); breastfeeding (Appendix 3);

**interactions:** Appendix 1

**Dosage:**
Initial test dose of 200 mg to detect hypersensitivity to quinidine

Arrhythmias, *by mouth*, **ADULT** 200–400 mg 3–4 times daily; increased if necessary in supraventricular tachycardia to 600 mg every 2–4 hours (maximum 3–4 g daily); frequent ECG monitoring required

**Adverse effects:**
hypersensitivity reactions, nausea, vomiting, diarrhoea, rashes, anaphylaxis, purpura, pruritus, urticaria, fever, thrombocytopenia, agranulocytosis after prolonged treatment, psychosis, angioedema, hepatotoxicity, respiratory difficulties; cardiac effects include myocardial depression, heart failure, ventricular arrhythmias and hypotension; cinchonism including tinnitus, impaired hearing, vertigo, headache, visual disturbances, abdominal pain, and confusion; lupus erythematosus-like syndrome

**VERAPAMIL HYDROCHLORIDE**

*Tablets,* verapamil hydrochloride 40 mg, 80 mg

**Note.**
Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation

**Injection** (*Solution for injection,* verapamil hydrochloride 2.5 mg/ml, 2-ml ampoule

**Uses:**
Supraventricular arrhythmias; angina (section 12.1)

**Contraindications:**
Hypotension, bradycardia, second- and third-degree atrioven- tricular block, sinoatrial block, sick sinus syndrome; cardiogenic shock; history of heart failure or significantly impaired left ventricular function (even if controlled by therapy); atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome; porphyria

**Precautions:**
First-degree atrioventricular block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment (Appendix 5); children (specialist
Verapamil and beta-blockers.
Both verapamil and beta-blockers have cardiodepressant activity, and their use together may lead to bradycardia, heart block and left ventricular failure, particularly in patients with myocardial insufficiency. Treatment with beta-blockers should be discontinued at least 24 hours before intravenous administration of verapamil

Dosage:
Supraventricular arrhythmias, by mouth, ADULT 40–120 mg 3 times daily
Supraventricular arrhythmias, by intravenous injection, ADULT 5–10 mg over 2 minutes (preferably with ECG monitoring); ELDERLY 5–10 mg over 3 minutes; in paroxysmal tachyarhythmias, further 5 mg may be given after 5–10 minutes if required

Adverse effects:
constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; with high doses, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect)

DISOPYRAMIDE

Tablets, 100mg

Use
Ventricular arrhythmias, especially after a myocardial infarction; supraventricular arrhythmias

Precautions
Discontinue if hypotension, hypoglycaemia, ventricular tachycardia, ventricular fibrillation or tardes de pointes develop; atrial flutter or tachycardia with partial block, bundle branch block, heart failure (avoid if severe); prostatic enlargement; glaucoma; hepatic and renal impairment; pregnancy and breast-feeding.

Containdications
Second- and third-degree heart block and sinus node dysfunction (unless pacemaker fitted); cardiogenic shock; severe uncompensated heart failure

Adverse reaction
Ventricular tachycardia, ventricular fibrillation or torsades de pointes (usually associated with prolongation of QRS complex or QT interval, myocardial depression, hypotension, AV block;
anti muscarinic effects include dry mouth, blurred vision, urinary retention, gastrointestinal irritation, psychosis, cholestatic jaundice, hypoglycaemia

**Dosage**

Oral, 300-800mg daily in divided doses

*Slow IV,* 2mg/kg over at least 5 minutes to a max. of 150mg, with ECG monitoring, followed immediately by either 200mg by mouth, then 200mg every 8 hours for 24 hours or 400mg micrograms/kg/hour by intravenous infusion; max. 300mg in first hour and 800mg daily.

### 12.3 Antihypertensive drugs

#### Management of hypertension

Treatment of hypertension should be integrated into an overall programme to manage factors that increase the risk of cardiovascular events (such as stroke and myocardial infarction). Treatment is often life-long. Hypertension was formerly classified as mild, moderate or severe, but a grading system is now preferred. Grade 1 hypertension is defined as 140–159 mmHg systolic blood pressure and 90–99 mmHg diastolic blood pressure, Grade 2 hypertension 160–179 mmHg systolic and 100–109 mmHg diastolic and Grade 3 hypertension more than 180 mmHg systolic and more than 110 mmHg diastolic. The goal of treatment is to obtain the maximum tolerated reduction in blood pressure.

Lifestyle changes should be introduced for all patients; they include weight reduction, reduction in alcohol intake, reduction of dietary sodium, stopping tobacco smoking, and reduction in saturated fat intake. The patient should eat a healthy nutritious diet including adequate fruit and vegetables and should exercise regularly. These measures alone may be sufficient in mild hypertension, but patients with moderate to severe hypertension will also require specific antihypertensive therapy.

#### Drug treatment of hypertension

Three classes of drug are used for first-line treatment of hypertension: thiazide diuretics, beta-adrenoceptor antagonists (beta-blockers), and angiotensin-converting enzyme (ACE) inhibitors. Calcium-channel blockers are considered first-line in specific populations only e.g. Africans or the elderly. Other classes of drugs may be used in certain situations.

Thiazide diuretics, such as hydrochlorothiazide (see also section 16.1), have been used as first-line antihypertensive therapy, and are particularly indicated in the elderly. They have few adverse effects in low doses, but in large doses they may cause a variety of unwanted metabolic effects (principally potassium depletion), reduced glucose tolerance, ventricular ectopic beats and impotence; they should be avoided in gout.

These effects can be reduced by keeping the dose as low as
possible; higher doses do not produce an increased reduction in blood pressure. Thiazides are inexpensive and, when used in combination, can enhance the effectiveness of many other classes of antihypertensive drug.

Beta-adrenoceptor antagonists (beta-blockers) such as atenolol are effective in all grades of hypertension, and are particularly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease, and heart block. Labetalol, is a beta blockers which has, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) such as enalapril and captopril are effective and well tolerated by most patients. They can be used in heart failure, left ventricular dysfunction and diabetic nephropathy, but should be avoided in renovascular disease and in pregnancy. The most common adverse affect is a dry persistent cough.

Dihydropyridine calcium-channel blockers such as nifedipine are useful for isolated systolic hypertension; in populations unresponsive to other antihypertensives (e.g. Africans) and in the elderly when thiazides cannot be used. Short-acting formulations of nifedipine should be avoided as they may evoke reflex tachycardia and cause large variations in blood pressure. Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries.Its use is confined to prevention of vascular spasm following subarachnoid haemorrhage.

Amlodipine, also resembles nifedipine and nicardipine in their effects and do not reduce myocardial contractility and they do not produce deterioration in heart failure. They have a longer duration of action and can be given once daily.

Drugs acting on the central nervous system are also effective antihypertensive drugs. In particular, methyldopa is effective in the treatment of hypertension in pregnancy. A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a stepwise manner until blood pressure is controlled.

Minoxidil should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. Hypertrichosis is troublesome and renders this drug unsuitable for women. Prazosin, has most post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia. It may however, causes a rapid reduction in blood pressure after the first dose and should be introduced with caution.

Hypertensive emergencies

In situations where immediate reduction of blood pressure is essential and treatment by mouth is not possible, intravenous infusion of sodium nitroprusside is effective. Over-rapid reduction in blood pressure is hazardous and can lead to reduced organ perfusion and cerebral infarction.

**Hypertension in pregnancy**
This is defined as a sustained diastolic blood pressure of 90 mmHg or more. Drug therapy for chronic hypertension during pregnancy remains controversial. If diastolic blood pressure is greater than 95 mmHg, methyldopa is the safest drug. Beta-blockers should be used with caution in early pregnancy, since they may retard fetal growth; they are effective and safe in the third trimester. ACE inhibitors are contraindicated in pregnancy since they may damage fetal and neonatal blood pressure control and renal function. Women who are taking these drugs and become pregnant should have their antihypertensive therapy changed immediately.

*Pre-eclampsia and eclampsia*. If pre-eclampsia or severe hypertension occurs beyond the 36th week of pregnancy, delivery is the treatment of choice. For acute severe hypertension in pre-eclampsia or eclampsia, intravenous hydralazine can be used. **Magnesium sulfate** (section 22.1) is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

**ATENOLOL**

*Tablets*. atenolol 50 mg, 100 mg

**Uses:**
- hypertension; angina (section 12.1); arrhythmias (section 12.2);
- migraine prophylaxis (section 7.2)

**Contraindications:**
- asthma or history of obstructive airways disease (unless no alternative, then with extreme caution and under specialist supervision);
- uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock;
- metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with alpha-blocker)

**Precautions:**
- avoid abrupt withdrawal especially in angina; may precipitate or worsen heart failure; pregnancy (Appendix 2); breastfeeding (Appendix 3); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment (Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia);
- history of hypersensitivity (increased reaction to allergens, also

reduced response to epinephrine (adrenaline)); myasthenia gravis; interactions: Appendix 1

Dosage:
Hypertension, by mouth, ADULT 50 mg once daily (higher doses rarely necessary)

Adverse effects:
gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation, abdominal cramp); fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances, including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rashes and dry eyes (oculomucocutaneous syndrome—reversible on withdrawal)

ENALAPRIL

Tablets, enalapril 5 mg, 20mg
Uses:
hypertension; heart failure (section 12.4)

Contraindications:
Hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2)

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 (reduce dose, see also Appendix 4); liver impairment (Appendix 5); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3); interactions: Appendix 1

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 (furosemide dose greater than 80 mg) 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 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

Dosage:
Hypertension by mouth, initially 5 mg once daily; if used in addition to diuretic, in elderly patients, or in renal impairment, initially 2.5 mg daily; usual maintenance dose 10–20 mg once daily; in severe hypertension may be increased to maximum 40 mg once daily

Adverse effects:
dizziness, headache; less commonly, nausea, diarrhoea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash and renal impairment; rarely, vomiting, dyspepsia, abdominal pain, constipation, glossitis, stomatitis, ileus, anorexia, pancreatitis, liver damage, chest pain, palpitations, arrhythmias, angioedema, bronchospasm, rhinorrhoea, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness or insomnia, pruritus, urticaria, alopecia, sweating, flushing, impotence, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, taste disturbance, tinnitus, blurred vision; electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity) reported

CAPTOPRIL

Tablets, 25mg, 12.5mg

Use
Mild to moderate essential hypertension alone or with thiazide therapy and severe hypertension resistant to other treatment; congestive heart failure; following myocardial infarction; diabetic nephropathy in insulin-dependent diabetes.

Precautions
ACE inhibitors need to be initiated with care in patients receiving diuretics; first dose may cause hypotension especially in patients taking high dose of diuretics, on a low sodium diet, on dialysis, dehydrated or in patients with heart failure. Use with caution in peripheral vascular disease or generalized atherosclerosis owing to risk of clinically silent renovascular disease. Renal function should be monitored before and during treatment and the dose should be reduced in renal impairment. ACE inhibitors should be used with care or avoided in patients with history of idiopathic or hereditary angioedema. Use with caution in breastfeeding.

Contraindication
Hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2)

Dosage
Hypertension, used alone, initially 12.5mg twice daily; if used in addition to diuretic, or elderly, initially 6.25mg twice daily (first dose at bedtime); usual maintenance dose 25mg twice daily; max. 50mg twice daily (rarely three times a day in severe hypertension)

Heart failure (adjunct), initially 6.25-12.5mg under close medical supervision; usual maintenance dose 25mg 2-3 times daily; usual max. 150mg daily

Prophylaxis after infarction in clinically stable patients with asymptomatic or symptomatic left ventricular dysfunction, initially 6.25mg starting as early as 3 days after infarct, then increase over several weeks to 150mg daily in divided doses.

Diabetic nephropathy, 75-100mg daily in divided doses; if further blood pressure reduction required other antihypertensives may be used in conjunction with captopril; in severe renal impairment, initially 12.5 mg twice daily.

**Adverse effects:**
Dizziness, headache; less commonly, nausea, diarrhoea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash and renal impairment; rarely, vomiting, dyspepsia, abdominal pain, constipation, glossitis, stomatitis, ileus, anorexia, pancreatitis, liver damage, chest pain, palpitations, arrhythmias, angioedema, bronchospasm, rhinorrhoea, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness or insomnia, pruritus, urticaria, alopecia, sweating, flushing, impotence, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, taste disturbance, tinnitus, blurred vision; electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity) reported

**LOSARTAN (SAD)**

*Tablet, 25mg, 50mg*

**Use**
Treatment of hypertension (HTN); treatment of diabetic nephropathy in patients with type 2 diabetes mellitus (noninsulin dependent, NIDDM) and a history of hypertension; stroke risk reduction in patients with HTN and left ventricular hypertrophy (LVH)

**Contraindications**
Hypersensitivity to losartan or any component of the formulation; hypersensitivity to other A-II receptor antagonists; bilateral renal artery stenosis; pregnancy

**Precautions**
Avoid use in the nursing mother, if possible, since it is postulated that losartan is excreted in breast milk. Hyperkalemia:
May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients dependent on renin-angiotensin-aldosterone system. Use with caution in patients with hepatic impairment; dose adjustment may be needed.

African-American patients: When used to reduce the risk of stroke in patients with.

**Adverse Reactions**
Chest pain, fatigue, diabetic nephropathy, hypoglycemia, diarrhea, urinary tract infection, anemia, weakness, back pain, hypertension to 12% diabetic nephropathy, cough, hypotension, orthostatic hypotension

**Dosage**
Oral: Hypertension: **CHILDREN** 6-16 years: 0.7 mg/kg once daily (maximum: 50 mg/day); adjust dose based on response; doses >1.4 mg/kg (maximum: 100 mg) have not been studied

**ADULTS:** Usual starting dose: 50 mg once daily; can be administered once or twice daily with total daily doses ranging from 25-100 mg

Patients receiving diuretics or with intravascular volume depletion: Usual initial dose: 25 mg

Nephropathy in patients with type 2 diabetes and hypertension:
Adults: Initial: 50 mg once daily; can be increased to 100 mg once daily based on blood pressure response

Stroke reduction (HTN with LVH): Adults: 50 mg once daily (maximum daily dose: 100 mg); may be used in combination with a thiazide diuretic

**LABETALOL**

*Injection, 5mg/ml; 20ml*

**Use**
Hypertension (including hypertension in pregnancy, hypertension in angina and hypertension following acute myocardia infarction); hypertension crisis; controlled hypertension in anaesthesia

**Precautions**
Pregnancy and breast feeding; reduce dose in hepatic impairment

**Contraindications**
Asthma and history of obstructive airway disease, uncontrolled heart failure , prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree AV
block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease, phaeochromocytoma

Use with extreme caution in patients with compensated heart

**Adverse effects**

Postural hypotension (avoid upright position during and for 3 hours after intravenous administration), tiredness, weakness, headache, rash, scalp tingling, difficult micturition, epigastric pain, nausea, vomiting, liver damage

**Dosage**

**CHILDREN:** Due to limited documentation of its use, labetalol should be initiated cautiously in pediatric patients with careful dosage adjustment and blood pressure monitoring.

Oral: Hypertension (unlabeled use): Initial: 1-3 mg/kg/day, in 2 divided doses; maximum: 10-12 mg/kg/day, up to 1200 mg/day

I.V., intermittent bolus doses of 0.3-1 mg/kg/dose has been reported.

For treatment of pediatric hypertensive emergencies, initial continuous infusions of 0.4-1 mg/kg/hour with a maximum of 3 mg/kg/hour have been used. Administration requires the use of an infusion pump.

**ADULTS:** Oral: Initial: 100 mg twice daily, may increase as needed every 2-3 days by 100 mg until desired response is obtained; usual dose: 200-400 mg twice daily; may require up to 2.4 g/day.

Usual dose range (JNC 7): 200-800 mg/day in 2 divided doses

I.V.: 20 mg (0.25 mg/kg for an 80 kg patient) IVP over 2 minutes; may administer 40-80 mg at 10-minute intervals, up to 300 mg total dose.

I.V. infusion (acute loading): Initial: 2 mg/minute; titrate to response up to 300 mg total dose, if needed. Administration requires the use of an infusion pump.

I.V. infusion (500 mg/250 mL D$_5$W) rates:

- 1 mg/minute: 30 mL/hour
- 2 mg/minute: 60 mL/hour
- 3 mg/minute: 90 mL/hour
- 4 mg/minute: 120 mL/hour
- 5 mg/minute: 150 mL/hour
- 6 mg/minute: 180 mL/hour

**PROPRANOLOL**

Tablets, 40mg

**Use**

Management of hypertension; angina pectoris; pheochromocytoma; essential tremor; supraventricular arrhythmias (such as...
atrial fibrillation and flutter, AV nodal re-entrant tachycardias, ventricular tachycardias (catecholamine-induced arrhythmias, digoxin toxicity); prevention of myocardial infarction; migraine headache prophylaxis; symptomatic treatment of hypertrophic subaortic stenosis

**Unlabeled**

Tremor due to Parkinson’s disease; ethanol withdrawal; ag-gressive behavior; antipsychotic-induced akathisia; prevention of bleeding esophageal varices; anxiety; schizophrenia; acute panic; gastric bleeding in portal hypertension; thyrotoxicosis; tetralogy of Fallot (TOF) hypercyanotic spells

**Precautions**

Propranolol crosses the placenta. Beta-blockers have been associated with bradycardia, hypotension, enters breast milk/ use caution, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring. Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms. Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment required.

**Contraindications**

Uncompensated congestive heart failure (unless the failure is due to tachyarrhythmias being treated with propranolol), cardiogenic shock, bradycardia or heart block (2nd or 3rd degree), pulmonary edema, severe hyperactive airway disease (asthma or COPD), Raynaud’s disease; pregnancy (2nd and 3rd trimesters)

**Adverse Effects**

Arterial insufficiency, AV conduction disturbance increased, bradycardia, cardiogenic shock, CHF, chest pain, hypotension, impaired myocardial contractility, mesenteric thrombosis (rare), Raynaud’s syndrome, syncope, amnesia, cognitive dysfunction, cold extremities, confusion, depression, dizziness, emotional lability, fatigue, hallucinations, hypersomnia, insomnia, lethargy, lightheadedness, memory loss (short-term), psychosis, vertigo, vivid dreams, alopecia, contact dermatitis, eczema-tous eruptions, erythema multiforme, exfoliative dermatitis, hyperkeratosis, nail changes, oculomucocutaneous reactions, pruritus, psoriasiform eruptions, rash, Stevens-Johnson syn-drome, toxic epidermal necrolysis, ulcers, ulcerative lichenoid, urticaria, hyper-/hypoglycemia, hyperkalemia, hyperlipidemia, bronchospasm, laryngospasm, pharyngitis, pulmonary edema, respiratory distress, wheezing

**METOPROLOL (SAD)**

*Tablets, 50mg. 100mg*

*Injection, 1mg/ml-5ml ampoule*

**Use**

Treatment of hypertension and angina pectoris; prevention
of myocardial infarction, atrial fibrillation, flutter, symptomatic treatment of hypertrophic subaortic stenosis

**Unlabeled**

Treatment of ventricular arrhythmias, atrial ectopy, migraine prophylaxis, essential tremor, aggressive behavior

**Precautions**

Bronchospastic disease, use with caution in patients with diabetes mellitus, use with caution in patients with compensated heart failure, hepatic impairment

**Contraindications**

Hypersensitivity to metoprolol or any component of the formulation; sick sinus syndrome; sinus bradycardia; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure; severe peripheral arterial disease; pheochromocytoma (without alpha blockade); pregnancy (2nd and 3rd trimesters)

**Adverse effects**

Bradycardia, hypotension, arterial insufficiency; chest pain, CHF, edema (peripheral), palpitation, syncope, gangrene (rare), dizziness, fatigue, depression, confusion, headache, insomnia, memory loss (short-term), nightmares, somnolence, pruritus, rash, psoriasis increased, alopecia (reversible; rare), libido decreased, Peyronie’s disease, diarrhea, constipation, flatulence, gastrointestinal pain, heartburn, nausea, xerostomia, dyspnea, bronchospasm, wheezing, rhinitis

**Dosage**

**ADULTS:**

- **Hypertension:** Oral: 100-450 mg/day in 2-3 divided doses, begin with 50 mg twice daily and increase doses at weekly intervals to desired effect; usual dosage range (JNC 7): 50-100 mg/day
- **Angina, SVT, MI prophylaxis:** Oral: 100-450 mg/day in 2-3 divided doses, begin with 50 mg twice daily and increase doses at weekly intervals to desired effect
- **Hypertension/ventricular rate control:** I.V. (in patients having nonfunctioning GI tract): Initial: 1.25-5 mg every 6-12 hours; titrate initial dose to response. Initially, low doses may be appropriate to establish response; however, up to 15 mg every 3-6 hours has been employed.
- **Congestive heart failure:** Oral (extended release): Initial: 25 mg once daily (reduce to 12.5 mg once daily in NYHA class higher than class II); may double dosage every 2 weeks as tolerated, up to 200 mg/day
- **Myocardial infarction (acute):** I.V.: 5 mg every 2 minutes for 3 doses in early treatment of myocardial infarction; thereafter give 50 mg orally every 6 hours 15 minutes after last I.V. dose and continue for 48 hours; then administer a maintenance dose of 100 mg twice daily.

**ELDERLY:** Oral: Initial: 25 mg/day; usual range: 25-300 mg/

day

**Administration: I.V.**

When administered acutely for cardiac treatment, monitor ECG and blood pressure. May administer by rapid infusion (I.V. push) over 1 minute or by slow infusion (ie, 5-10 mg of metoprolol in 50 mL of fluid) over ~30 minutes. Necessary monitoring for surgical patients who are unable to take oral beta-blockers (prolonged ileus) has not been defined. Some institutions require monitoring of baseline and postinfusion heart rate and blood pressure when a patient’s response to beta-blockade has not been characterized (ie, the patient’s initial dose or following a change in dose).

**HYDRAZINE HYDROCHLORIDE**

*Tablets,* hydralazine hydrochloride 25 mg

*Injection,* (Powder for solution for injection), hydralazine hydrochloride, 20-mg ampoule

**Uses:**

In combination therapy in moderate to severe hypertension, hypertensive crises; hypertension associated with pregnancy (including pre-eclampsia or eclampsia); heart failure (section 12.4)

**Contraindications:**

Idiopathic systemic lupus erythematosus, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, cor pulmonale, dissecting aortic aneurysm, porphyria

**Precautions:**

Hepatic impairment (Appendix 5); renal impairment (reduce dose, Appendix 4); coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilized); cerebrovascular disease; check acetylator status before increasing dose above 100 mg daily; test for antinuclear factor and for proteinuria every 6 months; pregnancy (Appendix 2); breastfeeding (Appendix 3); occasionally over-rapid blood pressure reduction even with low parenteral doses; **interactions:** Appendix 1

**Dosage:**

Hypertension, *by mouth,* ADULT 25 mg twice daily, increased if necessary to maximum 50 mg twice daily

Hypertensive crises (including during pregnancy), *by slow intravenous injection,* ADULT 5–10 mg diluted with 10 ml sodium chloride 0.9%; if necessary may be repeated after 20–30 minutes

Hypertensive crises (including during pregnancy), *by intravenous infusion,* ADULT initially 200–300 micrograms/minute; maintenance usually 50–150 micrograms/minute

**Reconstitution and administration.**
According to manufacturer’s directions

**Adverse effects:**
tachycardia, palpitations, postural hypotension; fluid retention; gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, rarely constipation; dizziness, flushing, headache; abnormal liver function, jaundice; systemic lupus erythematosus-like syndrome, particularly in women and slow acetylators; nasal congestion, agitation, anxiety, polyneuritis, peripheral neuritis, rash, fever, paraesthesia, arthralgia, myalgia, increased lacrimation, dyspnoea; raised plasma creatinine, proteinuria, haematuria; blood disorders including haemolytic anaemia, leukopenia, thrombocytopenia

**MINOXIDIL**

Tablets, 5 mg

**Use**
Management of severe hypertension (usually in combination with a diuretic and beta-blocker); treatment (topical formulation) of alopecia androgenetica in males and females

**Precautions**
Hypertrichosis: Inform patients of hair growth patterns before initiating therapy; may take 1-6 months for hypertrichosis to reverse itself after discontinuation of the drug.
Pericardial effusion/tamponade: May cause pericardial effusion progressing to tamponade.
Rapid blood pressure control: Rapid control of blood pressure can lead to syncope, CVA, MI, ischemia.
Sinus tachycardia: May increase oxygen demand and exacerbate angina pectoris.
Acute myocardial infarct (MI): Avoid use for a month after acute MI.
Cardiovascular disease: Use with caution in patients with pulmonary hypertension, CHF and/or ischemic disease.
Renal impairment: Use with caution in patients with significant renal impairment; renal failure and dialysis patients may require a smaller dose.

**Contraindications**
Hypersensitivity to minoxidil or any component of the formulation; pheochromocytoma; acute MI; dissecting aortic aneurysm

**Dosage**

**CHILDREN >12 years and Adults:** Hypertension: Oral: Initial: 5 mg once daily, increase gradually every 3 days (maximum: 100 mg/day); usual dose range (JNC 7): 2.5-80 mg/day in 1-2 divided doses

**ADULTS:** Alopecia: Topical: Apply twice daily; 4 months of therapy may be necessary for hair growth.

**ELDERLY:** Initial: 2.5 mg once daily; increase gradually
Adverse Effects
Peripheral edema, sodium and water retention, CHF, tachycardia, angina pectoris, pericardial effusion with or without tamponade, pericarditis, ECG changes (T-wave changes, rebound hypertension (in children after a gradual withdrawal), headache, fatigue, hypertrichosis, breast tenderness, gynecomastia, polymenorrhea, weight gain, nausea, vomiting, intermittent claudication, thrombocytopenia, decreased hematocrit (hemodilution), decreased hemoglobin (hemodilution), decreased erythrocyte count (hemodilution), leukopenia

HYDROCHLOROTHIAZIDE

Tablets, hydrochlorothiazide 25 mg, scored 50mg

Uses:
Alone in mild hypertension, and in combination with other drugs in moderate to severe hypertension; heart failure (section 12.4); oedema (section 16.1)

Contraindications:
Severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease

Precautions:
Renal and hepatic impairment (Appendices 4 and 5); pregnancy and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; interactions: Appendix 1

Dosage:
Hypertension, by mouth, ADULT 12.5–25 mg daily; ELDERLY initially 12.5 mg daily

Adverse effects:
fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias; hypokalaemia, hypomagnesaemia, hypernatraemia, hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis, pulmonary oedema, severe skin reactions)

METHYLDOPA

Tablets, methyldopa 250 mg

Uses:
Hypertension in pregnancy

**Contraindications:**
Depression; active liver disease; phaeochromocytoma, porphyria

**Precautions:**
History of hepatic impairment (Appendix 5); renal impairment (Appendix 4); blood counts and liver-function tests advised; history of depression; positive direct Coomb test in up to 20% of patients (affects blood cross-matching); interference with laboratory tests; pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

**Patient Advice**
May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage:**
Hypertension in pregnancy, *by mouth, ADULT* initially 250 mg 2–3 times daily; if necessary, gradually increased at intervals of 2 or more days, maximum 3 g daily

**Adverse effects:**
Tend to be transient and reversible, including sedation, dizziness, lightheadedness, postural hypotension, weakness, fatigue, headache, fluid retention and oedema, sexual dysfunction; impaired concentration and memory, depression, mild psychosis, disturbed sleep and nightmares; drug fever, influenza-like syndrome; nausea, vomiting, constipation, diarrhoea, dry mouth, stomatitis, sialadenitis; liver function impairment, hepatitis, jaundice, rarely fatal hepatic necrosis; bone-marrow depression, haemolytic anaemia, leukopenia, thrombocytopenia, eosinophilia; parkinsonism; rash (including toxic epidermal necrolysis); nasal congestion; black or sore tongue; bradycardia, exacerbation of angina; myalgia, arthralgia, paraesthesia, Bell palsy; pancreatitis; hypersensitivity reactions including lupus erythematosus-like syndrome, myocarditis, pericarditis; gynaecomastia, hyperprolactinaemia, amenorrhoea; urine darkens on standing

**NIFEDIPINE**

*Sustained-release tablets* (Modified-release tablets), nifedipine
10 mg

**Note.**
Sustained-release (prolonged-release) tablets are available for once daily administration. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation

**Uses:**
Hypertension

**Contraindications:**

Cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina; porphyria

**Precautions:**
stop if ischaemic pain occurs or existing pain worsens shortly after starting treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function; reduce dose in hepatic impairment (Appendix 5); diabetes mellitus; may inhibit labour; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1

**Dosage:**
Hypertension, *by mouth* (as sustained-release tablets), ADULT usual range 20–100 mg daily in 1–2 divided doses, according to manufacturer’s directions

**Note.**
Prescribers should be aware that different formulations of sustained-release tablets may not have the same clinical effect; if possible, the patient should be maintained on the same brandShort-acting formulations of nifedipine should be avoided in hypertension, particularly in patients who also have angina, since their use may be associated with large variations in blood pressure and reflex tachycardia, possibly leading to myocardial or cerebrovascular ischaemia

**Adverse effects:**
headache, flushing, dizziness, lethargy; tachycardia, palpitations; gravitational oedema (only partly responsive to diuretics); rash (erythema multiforme reported), pruritus, urticaria; nausea, constipation or diarrhoea; increased frequency of micturition; eye pain, visual disturbances; gum hyperplasia; paraesthesia, myalgia, tremor; impotence, gynaecomastia; depression; telangiectasis; cholestasis, jaundice

**NIMODIPINE (SAD)**

Capsule, 30mg

**Use**
Spasm following subarachnoid hemorrhage from ruptured intracranial aneurysms regardless of the patients neurological condition postictus (Hunt and Hess grades I-V)

**Contraindications**
Hypersensitivity to nimodipine or any component of the formulation

**Precautions**
Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient’s clinical condition. Intestinal pseudo-obstruction and ileus have been reported during therapy; use caution in patients with decreased Gl motility of a history of bowel obstruction. The most common side effect is peripheral edema; occurs within 2-3
weeks of starting therapy. Reflex tachycardia: May occur with use. Use with caution in patients with hepatic impairment
Adverse Reactions
Reductions in systemic blood pressure, headache, rash, diarrhea, abdominal discomfort
Dosage
Note: Capsules and contents are for oral administration ONLY.
Adults: Oral: 60 mg every 4 hours for 21 days start therapy within 96 hours after subarachnoid hemorrhage.
Administration: Oral
For oral administration, ONLY. If the capsules cannot be swallowed, the liquid may be removed by making a hole in each end of the capsule with an 18-gauge needle and extracting the contents into a syringe. If given via NG tube, follow with a flush of 30 mL NS.

AMLODIPINE

Tablets, 5mg
Use
Treatment of hypertension; treatment of symptomatic chronic stable angina, vasospastic (Prinzmetal's) angina (confirmed or suspected); prevention of hospitalization due to angina with documented CAD (limited to patients without heart failure or ejection fraction <40
Precaution
Angina/MI: Increased angina and/or MI have occurred with initiation or dosage titration of calcium channel blockers, symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition, peripheral edema; occurs within 2-3 weeks of starting therapy, reflex tachycardia, severe aortic stenosis, with hepatic impairment.
Adverse effects
Peripheral edema, flushing, palpitation headache, dizziness, fatigue, somnolence rash pruritus, male sexual dysfunction, nausea, abdominal pain, dyspepsia, gingival hyperplasia, muscle cramps, weakness, dyspnea, pulmonary edema
Dosage
Oral: CHILDREN 6-17 years: Hypertension: 2.5-5 mg once daily
ADULTS: Hypertension: Initial dose: 5 mg once daily; maximum dose: 10 mg once daily. In general, titrate in 2.5 mg increments over 7-14 days. Usual dosage range (JNC 7): 2.5-10 mg once daily.
Angina: Usual dose: 5-10 mg; lower dose suggested in elderly or hepatic impairment; most patients require 10 mg for adequate effect
ELDERLY: Dosing should start at the lower end of dosing

range due to possible increased incidence of hepatic, renal, or cardiac impairment. Elderly patients also show decreased clearance of amloidipine.

Hypertension: 2.5 mg once daily
Angina: 5 mg once daily

**Dosage adjustment in hepatic impairment:**
Angina: Administer 5 mg once daily.
Hypertension: Administer 2.5 mg once daily.

**Patient advice:**
Food: Grapefruit juice may modestly increase amloidipine levels.

**SODIUM NITROPRUSSIDE**

*Infusion* (Powder for solution for infusion), sodium nitroprusside, 50-mg ampoule

**Uses:**
Hypertensive crisis (when treatment by mouth not possible)

**Contraindications:**
Severe hepatic impairment; compensatory hypertension; severe vitamin B₁₂ deficiency; Leber optic atrophy

**Precautions:**
impaired pulmonary function; hypothyroidism; renal impairment (Appendix 4); ischaemic heart disease, impaired cerebral circulation; hyponatraemia; raised intracranial pressure; elderly; hypothermia; monitor blood pressure and blood-cyanide concentration, also blood-thiocyanate concentration if given for more than 3 days; avoid sudden withdrawal (reduce infusion over 15–30 minutes to avoid rebound effects); pregnancy; breastfeeding; **interactions:** Appendix 1

**Dosage:**
Hypertensive crisis, *by intravenous infusion*, ADULT initially 0.3 micrograms/kg/minute; usual maintenance dose 0.5–6 micrograms/kg/minute; maximum dose 8 micrograms/kg/minute; stop infusion if response unsatisfactory after 10 minutes at maximum dose; lower doses in patients already being treated with antihypertensives

Reconstitution and administration.
According to manufacturer’s directions

**Adverse effects:**
severe hypotension; effects associated with over-rapid reduction in blood pressure include headache, dizziness; retching, abdominal pain; perspiration; palpitations, apprehension, retrosternal discomfort; rarely reduced platelet count, acute transient phlebitis

Adverse effects associated with excessive concentration of cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, marked metabolic acidosis (discontinue infusion and give antidote, section 4.2.7)
12.3 Antihypertensive drugs

PRAZOSIN

Tablet, 1mg

Use
Treatment of hypertension

Unlabeled
Post-traumatic stress disorder (PTSD); benign prostatic hyperplasia; Raynaud’s syndrome

Contraindications
Hypersensitivity to quinazolines (doxazosin, prazosin, terazosin) or any component of the formulation; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors including sildenafil (>25 mg), tadalafil, or vardenafil

Precautions
Excretion in breast milk unknown/use caution. Discontinue if symptoms of angina occur or worsen. May cause significant orthostatic hypotension and syncope, especially with first dose;

Adverse Reactions
Dizziness, palpitation, edema, orthostatic hypotension, syncope, headache, drowsiness, vertigo, depression, nervousness, rash, decreased energy, nausea, vomiting, diarrhea, constipation, urinary frequency, weakness

Dosage
Oral:

CHILDREN (unlabeled use): Initial: 0.05-0.1 mg/kg/day in 3 divided doses; maximum: 0.5 mg/kg/day; ADULTS: Hypertension: Initial: 1 mg/dose 2-3 times/day; usual maintenance dose: 3-15 mg/day in divided doses 2-4 times/day; maximum daily dose: 20 mg

Hypertensive urgency: 10-20 mg once, may repeat in 30 minutes

PTSD (unlabeled use): Initial: 2 mg at bedtime; titrate as tolerated to 10-15 mg at bedtime

12.4 Drugs used in heart failure

Treatment of heart failure aims to relieve symptoms, improve exercise tolerance, reduce incidence of acute exacerbations, and reduce mortality. Drugs used to treat heart failure due to left ventricular systolic dysfunction include ACE inhibitors, diuretics, cardiac glycosides and vasodilators. In addition, measures such as weight reduction, moderate salt restriction, and appropriate exercise should be introduced.

The primary treatment of heart failure is with angiotensin-converting enzyme inhibitors (ACE inhibitors) such as enalapril which can be used in all stages of chronic heart failure to prevent further deterioration and progression of heart disease. A thiazide diuretic such as hydrochlorothiazide is used in the management of mild to moderate heart failure when the patient
has mild fluid retention and severe pulmonary oedema is not present; however thiazides are ineffective if renal function is poor. In these patients, and in more severe fluid retention, a loop diuretic such as furosemide (section 16.2) is required. In severe fluid retention, intravenous furosemide produces relief of breathlessness and reduces preload sooner than would be expected from the time of onset of diuresis. Hypokalaemia may develop, but is less likely with the shorter-acting loop diuretics than with the thiazides; care is needed to avoid hypotension. A combination of a thiazide and a loop diuretic may be required to treat refractory oedema. The combination often produces a synergistic effect on solute and water excretion, which relieves symptoms in the diuretic-resistant heart failure patient. However, the combination may produce excessive intravascular volume depletion and electrolyte disturbances including potentially life-threatening hypokalaemia.

The aldosterone antagonist spironolactone (section 16.3) may be considered for patients with severe heart failure who are already receiving an ACE inhibitor and a diuretic; a low dose of spironolactone (usually 25 mg daily) reduces symptoms and mortality rate in these patients. Close monitoring of serum creatinine and potassium is necessary with any change in treatment or in the patient's clinical condition.

Digoxin, a cardiac glycoside, increases the strength of cardiac muscle contractions and increases cardiac output. In mild heart failure, digoxin inhibits the sympathetic nervous system and produces arterial vasodilation. It produces symptomatic improvement, increases exercise tolerance, and reduces hospitalization, but it does not reduce mortality. It is considered for patients with atrial fibrillation and those who remain symptomatic despite treatment with an ACE inhibitor, a diuretic, and a suitable beta-blocker.

Vasodilators are used in heart failure to reduce systemic vascular resistance. Isosorbide dinitrate (section 12.1) produces mainly venous dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea. Hydralazine (section 12.3) produces mainly arterial vasodilation, which reduces left ventricular afterload, and increases stroke volume and cardiac output. Isosorbide dinitrate and hydralazine can be used in combination when an ACE inhibitor cannot be used.

Dopamine, an inotropic sympathomimetic, may be given for short periods in the treatment of severe heart failure. Dosage is critical; at low doses it stimulates myocardial contractility and increases cardiac output, however, higher doses (more than 5 micrograms/kg per minute) cause vasoconstriction, with a worsening of heart failure.

ENALAPRIL
Tablets, enalapril 2.5 mg

**Uses:**
Heart failure (with a diuretic); prevention of symptomatic heart failure and prevention of coronary ischaemic events in patients with left ventricular dysfunction; hypertension (section 12.3)

**Contraindications:**
Hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2)

**Precautions:**
use with diuretics; hypotension with first doses, especially in patients on diuretics, 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 (reduce dose, see also Appendix 4); liver impairment (Appendix 5); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3)

**Interactions:** Appendix 1

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 (furosemide dose greater than 80 mg daily) 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 stable

**Anaphylactoid reactions.**
Avoid enalapril during dialysis with high-flux polycrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom

**Dosage:**
Heart failure, asymptomatic left ventricular dysfunction, by mouth, adult, initially 2.5 mg daily under close medical supervision; usual maintenance dose 20 mg daily in 1–2 divided doses

**Adverse effects:**
dizziness, headache; less commonly, nausea, diarrhoea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash and renal impairment; rarely, vomiting, dyspepsia, abdominal pain, constipation, glossitis, stomatitis, ileus, anorexia, pancreatitis, liver damage, chest pain, palpitations, arrhythmias, angioedema, bronchospasm,
rhinorrhoea, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness or insomnia, pruritus, urticaria, alopecia, sweating, flushing, impotence, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, taste disturbance, tinnitus, blurred vision; electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity) reported

**DIGOXIN**

*Tablets*, digoxin 62.5 micrograms, 250 micrograms
*Oral solution*, digoxin 50 micrograms/ml
*Injection* (Solution for injection), digoxin 250 micrograms/ml, 2-ml ampoule

**Uses:**
- heart failure; arrhythmias (section 12.2)

**Contraindications:**
- hypertrophic obstructive cardiomyopathy (unless also severe heart failure); Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation; intermittent complete heart block; second-degree atrioventricular block

**Precautions:**
- recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; elderly (reduce dose); renal impairment (Appendix 4); avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions**: Appendix 1

**Dosage:**

Heart failure, **by mouth**, ADULT 1–1.5 mg in divided doses over 24 hours for rapid digitalization or 250 micrograms 1–2 times daily if digitalization less urgent; maintenance 62.5–500 micrograms daily (higher dose may be divided), according to renal function and heart rate response; usual range 125–250 micrograms daily (lower dose more appropriate in elderly)

Emergency loading dose, **by intravenous infusion** over at least 2 hours, ADULT 0.75–1 mg

**Note.**

Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks

**Adverse effects:**
- usually associated with excessive dosage and include anorexia, nausea, vomiting, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression; arrhythmias, heart block; rarely
rash, intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported

**Dopamine hydrochloride**

Dopamine hydrochloride is a complementary drug for inotropic support

*Concentrate for infusion* (Concentrate for solution for infusion), dopamine hydrochloride 40 mg/ml, 5-ml ampoule

**Uses:**
cardiogenic shock in myocardial infarction or cardiac surgery

**Contraindications:**
tachyarrhythmia, ventricular fibrillation; ischaemic heart disease; phaeochromocytoma; hyperthyroidism

**Precautions:**
correct hypovolaemia before, and maintain blood volume during treatment; correct hypoxia, hypercapnia, and metabolic acidosis before or at same time as starting treatment; low dose in shock due to myocardial infarction; history of peripheral vascular disease (increased risk of ischaemia of extremities); elderly;

**interactions:** Appendix 1

**Dosage:**
Cardiogenic shock, *by intravenous infusion* into large vein,

**ADULT** initially 2–5 micrograms/kg/minute; gradually increased by 5–10 micrograms/kg/minute according to blood pressure, cardiac output and urine output; seriously ill patients up to 20–50 micrograms/kg/minute

*Dilution and administration.* According to manufacturer’s directions

**Adverse effects:**
nausea and vomiting; peripheral vasoconstriction; hypotension with dizziness, fainting, flushing; tachycardia, ectopic beats, palpitations, anginal pain; headache, dyspnoea; hypertension particularly in overdosage

**Hydrochlorothiazide**

Hydrochlorothiazide is a representative thiazide diuretic. Various drugs can serve as alternatives

*Tablets,* hydrochlorothiazide 25 mg

**Uses:**
heart failure; hypertension (section 12.3); oedema (section 16.1)

**Contraindications:**
severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease

**Precautions:**
renal and hepatic impairment (Appendices 4 and 5); pregnancy

and breastfeeding (Appendices 2 and 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; interactions: Appendix 1

Dosage:
Heart failure, by mouth, ADULT initially 25 mg daily on rising, increasing to 50 mg daily if necessary; ELDERLY initially 12.5 mg daily

Adverse effects:
fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias; hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rashes, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions (pneumonitis, pulmonary oedema, severe skin reactions)

12.5 Antithrombotic drugs and myocardial infarction

Anticoagulants prevent thrombus formation or the extension of an existing thrombus. For further details see section 10.2 (drugs affecting coagulation).

Antiplatelet drugs also help to inhibit thrombus formation by decreasing platelet aggregation.

Thrombolytics (fibrinolytics) such as streptokinase are used to break up thrombi; they are used to treat acute myocardial infarction, extensive deep vein thrombosis, major pulmonary embolism and acute arterial occlusion.

Dipyridamole is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves

Myocardial infarction
Management of myocardial infarction includes two phases:
• initial management of the acute attack
• long-term management, including prevention of further attacks

Initial management
Oxygen (section 1.1.3) should be given to all patients, except those with severe chronic obstructive pulmonary disease. Pain and anxiety are relieved by slow intravenous injection of
an opioid analgesic such as morphine (section 2.2). Metoclopramide (section 17.2) may also be given by intramuscular injection to prevent and treat nausea and vomiting caused by morphine.

Acetylsalicylic acid 150–300 mg by mouth (preferably chewed or dispersed in water) is given immediately for its antiplatelet effect. Thrombolytic drugs such as streptokinase help to restore perfusion and thus relieve myocardial ischaemia; they should ideally be given within 1 hour of infarction (use after 12 hours requires specialist advice).

Nitrates (section 12.1) may also be given to relieve ischaemic pain. Early administration of beta-blockers such as atenolol (section 12.1) have been shown to reduce both early mortality and the recurrence rate of myocardial infarction; initial intravenous administration is followed by long-term oral treatment (unless the patient has contraindications).

ACE inhibitors (section 12.4) have also been shown to be beneficial in initial management (unless patient has contraindications) when given within 24 hours, and if possible continued for 5–6 weeks.

If arrhythmias occur, they should be treated aggressively, but the likelihood decreases rapidly over the first 24 hours after infarction. Ventricular fibrillation should be treated immediately with a defibrillator; if this is ineffective alone, the antiarrhythmic drug lidocaine (section 12.2) should be given. All patients should be closely monitored for hyperglycaemia; those with diabetes mellitus or raised blood-glucose concentration should receive insulin.

**Long-term management**

Acetylsalicylic acid should be given to all patients in a dose of 75–150 mg daily by mouth, unless it is contraindicated. The prolonged antiplatelet effect has been shown to reduce the rate of reinfarction.

Treatment with beta-blockers should be continued for at least 1 year, and possibly for up to 3 years. ACE inhibitors such as enalapril (section 12.4) should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction.

Nitrates (section 12.1) may be required for patients with angina. The use of statins (section 12.6) may also be considered in patients with high risk of recurrence.

**Stroke**

Stroke (cerebrovascular accident) may be ischaemic or haemorrhagic; precise diagnosis is essential, as management for
the two types of stroke is quite different. Primary prevention of both types of stroke includes reduction of high blood pressure, stopping smoking, weight reduction, and cholesterol reduction. Atrial fibrillation, acute myocardial infarction, and valvular disease may produce embolism and ischaemic stroke. Prophylaxis in patients at risk of ischaemic stroke includes oral anticoagulants such as warfarin (section 10.2) and antiplatelet drugs such as acetylsalicylic acid. Treatment of acute ischaemic stroke includes use of acetylsalicylic acid, anticoagulants such as heparin, and of thrombolytics, such as streptokinase. Streptokinase must be used with extreme caution due to risk of bleeding. Long-term therapy with acetylsalicylic acid reduces the risk of having another stroke. Antiplatelet and thrombolytic drugs are not used in the management of haemorrhagic stroke, as they may exacerbate bleeding. The main treatment is to normalize blood pressure. Acetylsalicylic acid is normally given for at least one year after coronary artery bypass surgery. It is also given to patients with prosthetic heart valves who have had cerebral embolism despite warfarin treatment.

**ACETYLSALICYLCIC ACID**

*Tablets, acetylsalicylic acid, 81 mg, Dispersible tablets (Soluble tablets), acetylsalicylic acid 75 mg*

**Uses:** prophylaxis of cerebrovascular disease or myocardial infarction; pyrexia, pain, inflammation (section 2.1.1); migraine (section 7.1)

**Contraindications:** hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (Reye syndrome, see section 2.1.1); active peptic ulceration; haemophilia and other bleeding disorders

**Precautions:** asthma; uncontrolled hypertension; pregnancy (Appendix 2); breastfeeding (Appendix 3); see also section 2.1.1; interactions: Appendix 1

**Dosage:** Prophylaxis of cerebrovascular disease or myocardial infarction, by mouth. ADULT 75–100 mg daily

**Adverse effects:** bronchospasm; gastrointestinal haemorrhage (rarely major), also other haemorrhage (for example subconjunctival); see also section 2.1.1

**STREPTOKINASE**
Streptokinase is a complementary drug; it is used in the management of myocardial infarction and thromboembolism.

**Injection** (Powder for solution for injection), streptokinase 1.5 million-unit vial

**Uses:**
- Life-threatening deep-vein thrombosis, pulmonary embolism,
- Acute arterial thromboembolism; thrombosed arteriovenous shunts; acute myocardial infarction

**Contraindications:**
- Recent haemorrhage, surgery (including dental), parturition, trauma; heavy vaginal bleeding; haemorrhagic stroke, history of cerebrovascular disease (especially recent or if residual disability); coma; severe hypertension; coagulation defects; bleeding diatheses, aortic dissection; risk of gastrointestinal bleeding such as recent history of peptic ulcer, oesophageal varices, ulcerative colitis; acute pancreatitis; severe liver disease; acute pulmonary disease with cavitation; previous allergic reactions

**Precautions:**
- Risk of bleeding from any invasive procedure, including injection; external chest compression; pregnancy (Appendix 2);
- Abdominal aneurysm or where thrombolysis may give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolization); diabetic retinopathy (small risk of retinal haemorrhage);
- Recent or concurrent anticoagulant treatment

**Dosage:**
- Thrombosis, **by intravenous infusion, ADULT** 250 000 units over 30 minutes, followed by 100 000 units every hour for 12–72 hours according to condition with monitoring of clotting parameters
- Myocardial infarction, **by intravenous infusion, ADULT** 1 500 000 units over 60 minutes
- Thrombosed arteriovenous shunts, consult manufacturer’s literature

**Adverse effects:**
- Nausea and vomiting; bleeding, usually limited to site of injection but internal bleeding including intracranial haemorrhage may occur (if serious bleeding occurs, discontinue infusion—coagulation factors may be required); hypotension, arrhythmias (particularly in myocardial infarction); allergic reactions including rash, flushing, uveitis, anaphylaxis; fever, chills, back or abdominal pain; Guillain-Barré syndrome reported rarely

**DIPYRIDAMOLE**

**Tablet,** dipyridamole 25 mg

**Uses:**
- As an adjunct to oral anticoagulatiun for prophylaxis of thromboembolism associated with prosthetic heart valves, modified-
release preparations are licensed for secondary prevention of ischaemic stroke and transient ischemic attacks

**Contraindications:**
no known contraindications. Use cautiously in hypotension

**Precautions:**
rapidly worsening angina, aortic stenosis, recent myocardial infarction heart failure, may exacerbate migraine, hypotension

**Dosage:**
by mouth, 300-600 mg daily in 3-4 divided doses before food.

**Adverse effects:**
nausea, vomiting, abdominal distress, dizziness, myalgia, throbbing headache, worsening symptoms of coronary heart disease, hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioedema, increased bleeding during or after surgery

### 12.5 Lipid-regulating drugs

The primary aim of therapy is to reduce progression of atherosclerosis and to improve survival in patients with established cardiovascular disease, to reduce premature cardiac morbidity and mortality in people at high risk of cardiovascular events and to prevent pancreatitis due to hypertriglyceridaemia. Before starting drug therapy dietary measures, reduction of blood pressure and cessation of smoking should be tried. The WHO Expert Committee on the Selection and Use of Essential Medicines recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. Beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG Co A) reductase inhibitors, often referred to as 'statins', (such as **simvastatin** and **atorvastatin**) are potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke and mortality (all causes), as well as the need for coronary bypass surgery. Satins are drugs of first choice for treating hypercholesterolaemia and fibrates (such as **gemfibrozil**) for treating hypertriglyceridaemia. Satins or fibrates can be used, either alone or together to treat mixed hyperlipaemia. The value of nicotinic acid as a lipid-lowering agent is limited by its side-effects, especially vasodilatation. In doses of 1.5 to 3 g daily it lowers both cholesterol and triglyceride concentrations by inhibiting synthesis.

**Simvastatin**

*Tablet,* 10 mg, 20 mg

**Uses:**

primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures; prevention of coronary events, need for revascularization procedures, and to slow progression of coronary atherosclerosis in patients with coronary heart disease and total cholesterol concentration of 5.5 mmol/litre or more

**Contraindications:**
Active liver disease (or persistently abnormal liver function tests) and in pregnancy (adequate contraception required during treatment and for 1 month afterwards) and breast-feeding

**Precautions:**
Discontinue if symptoms of myopathy or renal failure due to rhabdomyolysis develop. Should be used with caution in those with history of liver disease or with high blood pressure. Hypothyroidism should be managed adequately before starting treatment with satins. Patients should be advised to report unexplained muscle pain

**Dosage:**
- primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia, combined hyperlipidaemia, 10 mg daily at night, adjusted at intervals of not less than 4 weeks; usual range 10-80 mg once daily at night
- Homozygous familial hypercholesterolaemia, 40 mg daily at night or 80 mg daily in 3 divided doses (with largest dose at night)
- Coronary heart disease, initially 20 mg once daily at night, adjusted at intervals of not less than 4 weeks, max. 80 mg once daily

**NOTE**
Max. 10 mg daily with concomitant ciclosporin, fibrate or lipid-lowering dose of nicotinic acid

**Adverse effects:**
- Headache, altered liver-function tests, paraesthesia and gastro-intestinal effects including abdominal pain, flatulence, constipation, diarrhea, nausea and vomiting. Rash and hypersensitivity reactions.
- Myalgia, myositis and myopathy have been reported with satins; if myopathy is suspected and creatine kinase is markedly elevated (more than 5 times upper limit of normal), treatment should be discontinued; in patients at high risk of muscle effects, a satin should not be started if creatine kinase . . Also alopecia, anaemia, dizziness, peripheral neuropathy, hepatitis, jaundice, pancreatitis

**GEMFIBROZIL:**

Tablet, gemfibrozil 300 mg, 600 mg

Uses:
hyperlipidaemias of types 11a, 11b, 111, 1V and V in patients who have not responded adequately to diet and other appropriate measures; primary prevention of coronary heart disease in men aged 40-55 years with hyperlipidaemias that have not responded to diet and other appropriate measures.

Contraindications:
Alcoholism, hepatic impairment, gallstones; pregnancy, and breast-feeding

Precautions:
Lipid profile, blood counts, and liver function tests before initiating long-term treatment; renal impairment, preferably avoid use with statins (high risk of rhabdomyolysis); correct hypothyroidism before initiating treatment

Dose:
1.2 g daily, usually in 2 divided doses: range 0.9-1.5 g daily

Adverse effects:
Gastro-intestinal disturbances: also rash, dermatitis, pruritus, urticaria, impotence, headache, dizziness, blurred vision, cholestatic jaundice, angioedema, laryngeal oedema, atrial fibrillation, pancreatitis, myasthenia, myopathy, rhabdomyolysis, painful extremities, myalgia accompanied by increases in creatine kinase

Nicotinic Acid (Niacin)

Tablet, nicotinic acid, 600 mg

Uses:
treatment of hyperlipidaemias especially those associated with hypercholesterolaemia

Contraindications:
pregnancy, breast-feeding

Precautions:
renal impairment

Dosage:
initially 100-200 mg 3 times daily, gradually increased over 2-4 weeks to 1-2 g 3 times daily

NOTE, Doses of standard-release and modified-release formulations are not equivalent; when switching formulation initiate treatment with low dose and increase gradually as recommended.

Adverse effects:
flushing, dizziness, headache, palpitations pruritus ( prostaglandin-mediated symptoms can be reduced by low initial doses taken with meals, or by taking aspirin 75 mg 30 minutes before the dose); nausea, vomiting,
12.5 Lipid-regulating drugs

rarely impaired liver function and rashes
12.3 Antihypertensive drugs
Section 13:
DERMATOLOGICAL DRUGS (TOPICAL)

13.1 Antifungal medicines
13.2 Anti-infectives medicines
13.3 Anti-inflammatory and antipuritic
13.4 Astringents medicines
13.5 Medicines affecting skin differential and proliferation
13.6 Scabies and pediculicides
13.1 Antifungal drugs

RINGWORM

Benzoic acid and methylrosanilinium chloride (gentian violet) solution are inexpensive and effective fungistatic compounds for the treatment of dermatophyte infections such as ringworm. Minor skin lesions due to ringworm can be cleared with repeated applications of compound benzoic acid ointment (Whitfield ointment), which combines the fungistatic action of benzoic acid with the keratolytic action of salicylic acid. However, the most effective topical treatment for dermatophyte infections is a cream containing an imidazole such as miconazole, which is effective for long-established lesions but is more expensive than compound benzoic acid ointment. Extensive and generalized infections of the skin, nails and scalp should be treated systemically for several weeks with griseofulvin or ketoconazole (see section 6.3).

Scalp ringworm (tinea capitis) typically appears as a patch of scaling alopecia, or a swollen inflammatory area (tinea kerion). Mild forms may remit spontaneously at puberty. Infamed lesions should be treated systemically with griseofulvin. Application of miconazole cream may accelerate healing of scaly lesions.

Ringworm on the body (tinea corporis) can also be cleared with compound benzoic acid ointment or a topical imidazole such as miconazole. In resistant cases a 4-week course of oral griseofulvin is required.

Foot ringworm (tinea pedis or athlete’s foot) is usually treated topically. Compound benzoic acid ointment should be applied twice daily to all infected areas and all toe clefts for at least 4 weeks. Systemic therapy with griseofulvin or ketoconazole may be required if the foot is extensively infected. Tinea pedis commonly recurs and may be treated with miconazole cream. Severe weeping lesions respond to frequent soaking in solutions of 1:10 000 potassium permanganate, and systemic antifungals may also be needed.

Nail infections (onychomycosis, tinea unguium) are difficult to treat; fingernails may require 6 months treatment with oral griseofulvin and toenails may require 12 months or more of this treatment. Approximately 60% of nail infections either do not respond or relapse after treatment with griseofulvin.

Ringworm of the groin (tinea cruris) is usually limited to the skin of the inner thigh in contact with the scrotum. Flexural eczema, often superinfected with candida or bacteria, occurs in the same site. The latter is frequently treated with combined antifungal/corticosteroid preparations, but must not be treated with a corticosteroid alone, which will worsen the condition. An imidazole cream such as miconazole applied daily for 2 weeks is usually effective. Lesions unresponsive to topical
preparations can usually be cleared with a 4-week course of **griseofulvin**.

**CANDIDOSIS**
Candida can infect the oral cavity, the vagina or the skin. Cutaneous lesions tend to occur in patients with diabetes mellitus and some chronic debilitating conditions, including hypoparathyroidism and various congenital disorders of the immune system. The most severe infections of candida are now seen in patients with HIV infection. Cutaneous candidosis usually responds to **miconazole** cream as a twice daily application. Chronic candida paronychia, which can result ultimately in nail dystrophy, is more difficult to treat. Treatment should be based on determination of the underlying cause and its reduction or elimination; hands and folds of the nail must be kept dry and daily application of an imidazole cream for several months may be required, ensuring penetration of the cleft between the nail plate and the swollen skin around the nail.

**BENZOIC ACID WITH SALICYLIC ACID**

*Ointment*, benzoic acid 6%, salicylic acid 3%

**Uses:**
Mild dermatophyte infections, particularly tinea pedis and tinea corporis

**Administration:**
Fungal skin infections, *apply* twice daily until the infected skin is shed (usually at least 4 weeks)

**Adverse effects:**
Occasionally localized, mild inflammatory reaction

**MICONAZOLE NITRATE**

Miconazole is a representative topical antifungal. Various drugs can serve as alternatives

*Cream*, miconazole nitrate 2%

*Ointment*, miconazole nitrate 2%

**Uses:**
superficial fungal infections due to dermatophytes and yeasts, and secondary infections caused by Gram-positive cocci, including ringworm, intertrigo, candida napkin rash, paronychia, and pityriasis versicolor

**Administration:**
Skin infections; *apply* twice daily to clean dry lesions, continuing for at least 10 days after the condition has cleared
Nail infections; *apply* 1–2 times daily

**Adverse effects:**

Occasional local irritation and burning, also contact dermatitis; discontinue if sensitization occurs

**CLOTRIMAZOLE**

*Cream vaginal, 1%*

**Use**
Treatment of susceptible fungal infection, including oropharyngeal candidiasis, dermatophytoses, superficial mycoses, and cutaneous candidiasis, as well as vulvovaginal candidiasis

**Precautions**
Clotrimazole should not be used for treatment of systemic fungal infection, avoid contact with eyes

**Adverse Effects**
Mild burning and irritation, stinging to skin or vaginal area, vulvar burning

**Dosage**
Insert: 1 applicatorful vaginal cream daily (preferably at bedtime) for 7 consecutive days

**KETOCONAZOLE**

*Tablets, 200mg*

**Use**
Systemic: Treatment of susceptible fungal infections, including candidiasis, oral thrush, blastomycosis, histoplasmosis, paracoccidioidomycosis, coccidioidomycosis, chromomycosis, candiduria, chronic mucocutaneous candidiasis, as well as certain recalcitrant cutaneous dermatophytoses

**Precautions**
Enter breast milk/not recommended

**Contraindications**
Hypersensitivity to ketoconazole or any component of the formulation; CNS fungal infections (due to poor CNS penetration); coadministration with ergot derivatives or cisapride is contraindicated due to risk of potentially fatal cardiac arrhythmias

**Adverse Reactions**
Oral:
Pruritus, nausea/vomiting, abdominal pain

**Dosage**
Oral:
Fungal infections:
*CHILDREN* ≤2 years: 3.3-6.6 mg/kg/day as a single dose for 1-2 weeks for candidiasis, for at least 4 weeks in recalcitrant dermatophyte infections, and for up to 6 months for other systemic mycoses

*ADULTS*: 200-400 mg/day as a single daily dose for durations as stated above

Nystatin
Topical ointment, 10%
Use
Treatment of susceptible cutaneous, mucocutaneous, and oral cavity fungal infections normally caused by the *Candida* species

**Contraindications**
Hypersensitivity to nystatin or any component of the formulation

**Adverse Reactions**
Contact dermatitis, Stevens-Johnson syndrome

**Dosage**
Mucocutaneous infections: **CHILDREN** and **ADULTS**: Topical: Apply 2-3 times/day to affected areas; very moist topical lesions are treated best with powder

### 13.2 Anti-infective (antibacterial) drugs

Staphylococcal infections of the skin such as impetigo, folliculitis, and furunculosis and streptococcal infections such as cellulitis and erysipelas are very common where the climate is hot and humid, where standards of hygiene are compromised, and in immunodeficient patients.

In all skin infections, an important part of treatment is cleansing and thorough drying. Washing with soap and water will often help to prevent infection. Light localized infections can often be treated effectively with an antiseptic solution such as **chlorhexidine** (section 15.1). Superficial crusts should be gently washed with soap and water or a weak solution of 0.01% solution of **potassium permanganate**. Infected burns should be treated with **silver sulfadiazine**, which is bactericidal against both Gram-positive and Gram-negative organisms.

An ointment containing 2% mupirocin, which is active against Gram-positive bacteria, is of value, particularly in impetigo. To prevent the development of resistance, mupirocin should not be used for more than 10 days. Topical preparations containing **neomycin** and **bacitracin** are also widely used but these carry a risk of sensitization particularly with continued or repeated use.

Topical use of preparations containing antimicrobials which are widely used systemically should be avoided. These include penicillins, sulfonamides, streptomycin and gentamicin, which should be reserved for the systemic treatment of infections because of the possibility of inducing sensitivity and favouring the emergence of resistant organisms. Only widespread superficial or deep-seated infections associated with fever require treatment with a systemic antibiotic (sections 6.2.1 and 6.2.2).

Whenever possible, the choice of an antimicrobial should be based on the results of sensitivity tests.

**METHYLROSANILINIUM CHLORIDE**

Gentian violet; Crystal violet
Methylrosanilinium chloride is a representative topical anti-
infective drug. Various drugs can serve as alternatives
Cutaneous solution, methylrosanilinium chloride 0.5%
Tincture, methylrosanilinium chloride 0.5%

**Uses:**
superficial fungal and bacterial infections

**Contraindications:**
excoriated or ulcerated lesions, broken skin, mucous mem-
branes

**Administration:**
Skin infections, apply 2 or 3 times daily for 2–3 days

**Adverse effects:**
severe irritation (discontinue treatment); temporary staining
of skin, permanent staining of fabrics; *animal* carcinogenicity
(restricted use in some countries)

**ACRIFLAVINE**

Solution, 0.1%
Use
Skin disinfectant

**POTASSIUM PERMANGANATE**

Cutaneous solution, potassium permanganate 1:10 000 (0.01%
solution)

*Note.*
Potassium permanganate is sometimes supplied as an aque-
ous stock solution of 1 in 1000 (0.1%) for dilution before use

**Uses:**
¬ wet dressings to assist healing of suppurating superficial
¬ wounds, tropical ulcers, tinea pedis, pemphigus, impetigo

**Contraindications:**
¬ avoid occlusive dressings

**Precautions:**
¬ irritant to mucous membranes

**Administration:**
¬ Suppurating superficial wounds and tropical ulcers, wet
dressings of 1:10 000 (0.01%) solution, changed 2 or 3 times
daily; tropical ulcers also require treatment for 2–4 weeks with
procaine benzylpenicillin (section 6.2.1.1)
¬ Tinea pedis, soak severe weeping lesions in 1:10 000 (0.01%)
solution every 8 hours
¬ Pemphigus, soak compresses in 1:10 000 (0.01%) solution
and apply every 4 hours
¬ Impetigo, superficial crusts should be gently separated with a
1:10 000 (0.01%) solution

**Adverse effects:**
local irritation; skin and fabrics stained brown

**NEOMYCIN WITH BACITRACIN**

Bacitracin is a representative topical antibacterial. Various drugs can serve as alternatives

*Ointment*, neomycin sulfate 5 mg/bacitracin zinc 500 units/g

**Uses:**
Superficial bacterial infections of the skin due to staphylococci and streptococci

**Precautions:**
Avoid application to substantial areas of skin or to broken skin (risk of significant systemic absorption); overgrowth of resistant organisms on prolonged use

**Administration:**
Bacterial skin infections, **adult and child over 2 years** apply thin layer 3 times daily

**Adverse effects:**
Sensitization, especially to neomycin, causing reddening and scaling; anaphylaxis reported rarely; systemic absorption leading to irreversible ototoxicity, particularly in children, the elderly, and in renal impairment

**SILVER SULFADIAZINE**

*Cream*, silver sulfadiazine 1%

**Uses:**
Prophylaxis and treatment of infection in burns

**Contraindications:**
Hypersensitivity to sulfonamides; pregnancy (Appendix 2); neonates

**Precautions:**
renal or hepatic impairment; G6PD deficiency; breastfeeding (Appendix 3)

**Administration:**
Infection in burns, **apply** using aseptic technique daily (more frequently if volume of exudate is large) whilst there is a possibility of infection, or until healing is complete

**Adverse effects:**
Allergic reactions include rashes, burning and itching; argyria and sulfonamide-induced systemic toxicity, including blood disorders following application to large areas or prolonged use; transient leukopenia reported

13.3 **Anti-inflammatory and antipruritic drugs**
CONTACT DERMATITIS
Contact dermatitis can result from an allergic or irritant skin reaction. Removal of the substance provoking the reaction is the first step in treating this condition. Mild cases of contact dermatitis can be treated with topical hydrocortisone which suppresses inflammation. A short course of oral prednisolone or a topical corticosteroid such as betamethasone should be considered for more severe cases and for suppression of severe acute reactions associated with blistering, exudation and oedema. Soaking in clean water or mild saline solution is recommended in the acute stages of severe dermatitis.

PRURITUS
Pruritus or itching is a common symptom of many skin diseases. However, contact with certain substances, conditions that dry the skin, stress, and extremes of temperature may also be a cause. Thus, an important part of treatment is to eliminate or minimize the reason for the irritation.

Corticosteroids, such as hydrocortisone or betamethasone applied topically, can give relief. Soothing baths or the application of an emollient cream may also be helpful; the value of calamine lotion is uncertain. Systemic antihistamines, such as oral chlorphenamine (section 3.1), may relieve generalized pruritus.

ATOPIC DERMATITIS
Atopic dermatitis (or eczema) is a common skin disorder, which mainly occurs in infants and children; it is associated with intense itching, with areas of red skin. Topical hydrocortisone should be applied in short courses of 1–2 weeks to treat even mild areas of involvement. The use of betamethasone should be considered in the treatment of persistent localized dermatitis in adults. Topical antihistamines are not effective and should be avoided because of the risk of sensitization. However, a sedative antihistamine can be given at night to calm pruritus and facilitate sleep (section 3.1). A secondary infection, often involving Staphylococcus aureus, may be responsible for exacerbations; in such cases, an oral antibiotic such as erythromycin can be given for 7–10 days (section 6.2.2.4).

ICHTHYOSIS
In ichthyosis, emollients such as aqueous creams and emulsifying creams should be applied daily (or more frequently in severe cases) to affected skin. The addition of a keratolytic, such as salicylic acid 5% can be helpful.

LICHEN PLANUS
Lichen planus is a chronic, papular, pruritic skin eruption that
occurs typically in middle age and later life; the condition is
often mild and may need no treatment. In more severe cases,
when the underlying cause cannot be identified, a topical cor-
ticosteroid offers the only prospect of remission.

**PITYRIASIS ROSEA**
In pityriasis rosea, a common self-limiting dermatosis that is
probably of infective origin, calamine lotion helps to relieve
pruritus in most cases. If it does not, topical application of
hydrocortisone in a concentration not exceeding 1% is worth
trying.

**CALAMINE**
Calamine is a representative topical antipruritic. Various drugs
can serve as alternatives
Lotion (Cutaneous suspension), calamine 8% (USP), 15%
(BP)
Uses:
mild pruritus
Administration:
Mild pruritus, apply liberally 3–4 times daily

**Corticosteroids**

**BETAMETHASONE (SAD)**
Betamethasone (as valerate) 0.1% is a representative potent
topical corticosteroid. Various drugs can serve as alterna-
tives
Cream, betamethasone (as valerate) 0.1%
Ointment, betamethasone (as valerate) 0.1%

Uses:
severe inflammatory skin conditions including contact dermati-
tis, atopic dermatitis (eczema), seborrhoeic dermatitis, lichen
planus, psoriasis of the scalp, hands and feet, intractable
pruritus

Contraindications:
unreated skin infections or broken skin, rosacea, acne, perioral
dermatitis

Precautions:
children (avoid prolonged use); adrenal suppression if used on
a large area of the body or for a long time, particularly with an
occlusive dressing or on broken skin; avoid use on the face for
more than 7 days; secondary infection requires treatment with
an appropriate antimicrobial

Administration:
Inflammatory skin conditions, ADULT and CHILD over 2 years
of age, apply small quantity to the affected area 1–2 times daily until improvement occurs, then less frequently

**Adverse effects:**
exacerbation of local infection; local atrophic changes particularly on the face and in skinfolds, characterized by thinning of the dermis, depigmentation, dilatation of superficial blood vessels and formation of striae; perioral dermatitis; acne at site of application; suppression of the hypothalamic-pituitary-adrenal axis with prolonged or widespread use (particularly under occlusion)

**HYDROCORTISONE ACETATE**

Hydrocortisone acetate is a representative mild topical corticosteroid. Various drugs can serve as alternatives

*Cream*, hydrocortisone acetate 1%

*Ointment*, hydrocortisone acetate 1%

**Uses:**
contact dermatitis, atopic dermatitis (eczema), lichen planus; intractable pruritus and phototoxic reactions, including polymorphous light eruptions and actinic prurigo; short-term treatment of psoriasis of the face and flexures

**Contraindications:**
untreated skin infections or broken skin; rosacea, acne, perioral dermatitis

**Precautions:**
children (avoid prolonged use); occlusive dressings increase penetration into keratinized lesions (use occlusive dressings only at night and for no longer than 2 days; avoid use on weeping lesions); secondary infection requires treatment with an appropriate antimicrobial

**Administration:**
Inflammatory skin conditions, apply a small quantity to the affected area 1–2 times daily until improvement occurs, then less frequently

**Adverse effects:**
exacerbation of local infection; atrophic changes (see under Betamethasone) less likely with mild corticosteroids, but infants and children particularly susceptible

**XYLOPROCT**

*Aluminium acetate 3.5%, hydrocortisone acetate 0.275%, lidocaine 10%, zinc oxide 18%*

**Use**
Haemorrhoids

**Dosage**
Treatment is usually symptomatic and use of a locally applied cream is appropriate for short periods

Adverse effects
Local anaesthetics can cause stinging initially, prolong use can cause atrophy of the anal skin

13.4 Astringents

Potassium permanganate (section 13.2) may be used in the same way as a topical astringent used as an antiseptic for various skin conditions including suppurating superficial wounds and tropical ulcers, and the lesions produced by pemphigus and impetigo.

Zinc Oxide paste is also applied as an astringent

Zinc oxide
Cream 15g

Use
Pruritus, eczema

Precaution
Use combined with castor oil in infants

13.5 Drugs affecting skin differentiation and proliferation

Acne vulgaris

Acne is a disorder of the pilosebaceous follicles and typically first appears during puberty when androgenic stimulation triggers excessive production of sebum. Mild acne is characterized by comedones and a few pustules which heal without scarring, and usually responds to topical therapy alone. In moderate acne, where there are more extensive pustules causing mild scarring, oral antibiotics such as a tetracycline or erythromycin (section 6.2.2.4) are commonly used. In severe acne, widespread pustules are accompanied by nodular abscesses and cysts, requiring treatment with estrogens, antiandrogens, or retinoids. Since scarring of the skin resulting from severe nodular acne causes major distress, acne should always be treated as soon as possible. Exposure to substances suspected of causing or aggravating the condition should be avoided. Systemic treatment must be continued for several months before a response can be anticipated. During this time, topical preparations should be applied to the affected areas to prevent the development of new lesions.

Benzoyl peroxide is a keratolytic drug with bacteriostatic activity against Propionibacterium acnes; treatment is usually started at a lower strength and increased as tolerance develops to the initial irritant reaction.

Topical antibiotics such as clindamycin are widely used in inflammatory acne. However, treatment must be maintained

for 2 to 3 months before any benefit is seen and this prolonged course carries the risk of selection and spread of antibiotic-resistant organisms.

**BENZOYL PEROXIDE**

*Cream*, benzoyl peroxide 5%

*Lotion* (Cutaneous suspension), benzoyl peroxide 5%

**Uses:**
mild to moderate acne and as an 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

**Administration:**
Acne, initially apply to clean skin on alternate days, increasing frequency to 1–2 times daily as tolerance to irritant effect develops

**Adverse effects:**
Initial irritation common but subsides with continued use; rarely, contact sensitivity occurs, occasionally even 1 application can cause severe irritation; may bleach fabrics, hair and skin

**PODOPHYLLUM RESIN**

An example of an application to treat warts. Various drugs can serve as alternatives

*Solution* (Cutaneous solution), podophyllum resin 10–25%

**Uses:**
external anogenital warts; plantar warts

**Contraindications:**
pregnancy (Appendix 2); breastfeeding; children

**Precautions:**
avoid use on large areas, mucous membranes; irritant to eyes; avoid contact with normal skin

**Administration:**
*NOTE.*
Medical supervision required

Warts, adult apply carefully to warts, avoiding contact with normal tissue; rinse off after 1–4 hours; may be repeated at weekly intervals but no more than 4 times in all; only few warts to be treated at any one time

**Adverse effects:**
Systemic effects resulting from cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea; also transient leukopenia and thrombocytopenia; renal failure; delayed
neurotoxicity including visual and auditory hallucinations, delusions, disorientation, confusion and delirium following excessive application

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; therefore the entire household must be treated at the same time to prevent reinfection. It is not necessary to take a bath before treatment with an acaricide, but all clothing and bedding should be washed to prevent reinfection. **Benzyl benzoate** is an inexpensive scabicide. It must be applied to all skin surfaces, from the scalp to the soles of the feet, avoiding contact with the eyes; it is too irritant for use on children. **Permethrin** and **Lindane** is less irritant and more effective than benzyl benzoate, but also more expensive; it may be used on children.

**PEDICULOSIS**

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 eye lashes 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. Head and body lice are readily treated with **permethrin**; **Benzyl benzoate** may be used for all lice infestations.

**BENZYL BENZOATE**

Benzyl benzoate is a representative parasiticide. Various drugs can serve as alternatives

*Lotion* (Cutaneous suspension), benzyl benzoate 25%

**Uses:**
scabies; head, body and pubic lice

**Precautions:**
do not use on inflamed or broken skin; avoid contact with eyes and mucous membranes; not recommended for children; breastfeeding (withhold during treatment)

**Administration:**
Scabies, **ADULT**, apply from neck down at night for 2 nights; on each occasion wash off after at least 24 hours
Pediculosis, **ADULT**, apply to affected area and wash off 24
hours later; further applications possibly needed after 7 and 14 days

**Adverse effects:**
Local irritation, particularly in children

**PERMETHRIN**

*Cream,* permethrin 5%
*Lotion (Cutaneous suspension),* permethrin 1%

**Uses:**
Scabies; head and body lice

**Precautions:**
Do not use on inflamed or broken skin; avoid contact with eyes; breastfeeding (withhold during treatment)

**Administration:**
Scabies and body lice *apply* cream over whole body and wash off after 8–12 hours
Head lice, *apply* lotion to clean damp hair and rinse off after 10 minutes

**Adverse effects:**
Local irritation; rarely rashes and oedema

**LINDANE**

*Cream,* 1%, 50g
*Shampoo,* 1%- 200mls
*Lotion,* 1%

**Use**
Treatment of *Sarcoptes scabiei* (scabies), *Pediculus capitis* (head lice), and *Phthirus pubis* (crab lice); FDA recommends reserving lindane as a second-line agent or with inadequate response to other therapies

**Contraindications**
Hypersensitivity to lindane or any component of the formulation; uncontrolled seizure disorders; crusted (Norwegian) scabies, acutely-inflamed skin or raw, weeping surfaces or other skin conditions which may increase systemic absorption

**Precautions**
May be associated with severe neurologic toxicities (contraindicated in premature infants and uncontrolled seizure disorders). Avoid contact with face, eyes, mucus membrane, and urethral meatus.

**Adverse Reactions**
Cardiac arrhythmia, ataxia, dizziness, headache, restlessness, seizure, pain, alopecia, contact dermatitis, skin and adipose tissue may act as repositories, eczematous eruptions, pruritus, and urticaria; aplastic anemia, hepatitis

**Dosage**

**CHILDREN AND ADULTS:** Topical:
Scabies: Apply a thin layer of lotion and massage it on skin from the neck to the toes; after 8-12 hours, bathe and remove the drug.

Head lice, crab lice: Apply shampoo to dry hair and massage into hair for 4 minutes; add small quantities of water to hair until lather forms, then rinse hair thoroughly and comb with a fine tooth comb to remove nits. Amount of shampoo needed is based on length and density of hair; most patients will require 30 mL (maximum: 60 mL).

**Administration**: Topical
For topical use only. Caregivers should apply with gloves (avoid natural latex, may be permeable to lindane). Rinse off with warm (not hot) water.

Lotion: Apply to dry, cool skin; do not apply to face or eyes. Wait at least 1 hour after bathing or showering (wet or warm skin increases absorption). Skin should be clean and free of any other lotions, creams, or oil prior to lindane application.

Shampoo: Apply to clean, dry hair. Wait at least 1 hour after washing hair before applying lindane shampoo. Hair should be washed with a shampoo not containing a conditioner; hair and skin of head and neck should be free of any lotions, oils, or creams prior to lindane application.

**Patient Education**
For external use only. Do not apply to face and avoid getting in eyes. Do not apply immediately after hot, soapy bath. For scabies, apply from neck to toes. Bathe to remove drug after 8-12 hours. For head lice or crab lice, massage into dry hair for 4 minutes; add water to hair to form lather, then rinse thoroughly. Clothing and bedding must be washed in hot water or dry cleaned to kill nits. Wash combs and brushes with lindane shampoo and thoroughly rinse. May need to treat all members of household and all sexual contacts concurrently. Report if condition persists or infection occurs. Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Do not breast-feed.
Section 14: Diagnostics

14.1 Radiocontrast media
Diagnostics

14.1 Radiocontrast media

Radiographic contrast media are needed for delineating soft tissue structures such as blood vessels, stomach, bowel loops and body cavities not otherwise visualized by standard X-ray examination. The contrast media in this group containing heavy atoms (metal or iodine) absorb a significantly different amount of X-rays than the surrounding soft tissue, thereby making the examined structures visible on radiographs.

**Barium sulfate** is a metal salt which is used to delineate the gastrointestinal tract. It is not absorbed by the body and does not interfere with stomach or bowel secretion or produce misleading radiographic artefacts. Barium sulfate may be used in either single- or double-contrast techniques or computer-assisted axial tomography. For double contrast examination gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide or by using separate gas-producing preparations based on sodium bicarbonate. Air administered through a gastrointestinal tube can be used as an alternative to carbon dioxide to achieve a double-contrast effect.

**Amidotrizoates** (meglumine amidotrizoate and sodium amido trizoates) are iodinated ionic monomeric organic compound. This salt has been used alone in diagnostic radiography including computer-assisted axial tomography but a mixture. Amidotrizoates are used in a wide range of procedures including urography and examination of the gallbladder, biliary ducts and spleen. Owing to the high osmolality and the resulting hypertonic solutions, is associated with a high incidence of adverse effects. Radiodensity depends on iodine concentration, and osmolality depends on number of particles in a given weight of solvent. The osmolality for a given radiodensity can be reduced by using an ionic dimeric medium such as meglumine iotroxate which contains twice the number of iodine atoms in a. **Meglumine iotroxate** is excreted into the bile after intravenous administration and used for cholecystography and cholangiography.

**HYPERSENSITIVITY**

Anaphylactoid reactions to iodinated radiocontrast media are more common with ionic, high osmolality compounds. Patients with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to contrast media, and those receiving beta-adrenoceptor antagonists (beta-blockers) are at increased risk. Non-ionic media are preferred for these patients and beta-blockers should be discontinued if possible.
Barium sulfate
Oral suspension (or Rectal suspension), barium sulfate 30 to 200% w/v

Uses:
Radiographic examination of the gastrointestinal tract (see notes above)

Contraindications:
Intestinal obstruction, conditions such as pyloric stenosis or lesions which predispose to obstruction; intestinal perforation or conditions with risk of perforation, such as acute ulcerative colitis, diverticulitis, or after rectal or colonic biopsy, sigmoidoscopy or radiotherapy

Precautions:
Adequate hydration after procedure to prevent severe constipation

Dosage:
Radiographic examination of gastrointestinal tract, ADULT and CHILD, route and dosage depend on procedure and preparation used (consult manufacturer’s literature)

Administration.
Only by specialist radiographers, according to manufacturer’s directions

Adverse effects:
Constipation or diarrhoea, abdominal cramps and bleeding; perforation of bowel resulting in peritonitis, adhesions, granulomas and high mortality rate; electrocardiographical changes—may occur with rectal administration; pneumonitis or granuloma formation—following accidental aspiration into lungs

Meglumine Amidotrizoate/Sodium Ammidotrizoate-Urografin 76%

Meglumine Amidotrizoate/Sodium Ammidotrizoate are representative iodinated ionic dimeric contrast medium. Various media can serve as alternatives. It is a complementary drug Injection (Solution for injection), (as Meglumine Amidotrizoate/ Sodium Ammidotrizoate ), 140-420mg/ml, 20-ml bottle

Uses:
Urography, venography, operative cholangiography, splenoporto graphy, arthrography, discography; computer assisted axial tomography.

Contraindications:
Hypersensitivity to iodine-containing compounds

Precautions:
history of allergy, atopy or asthma; severe hepatic impairment; renal impairment (Appendix 4); dehydration—correct fluid and electrolyte balance before administration; multiple myeloma

(risk if dehydrated, may precipitate fatal renal failure); cardiac disease, hypertension, phaeochromocytoma, sickle-cell disease, hyperthyroidism, elderly, debilitated or children—increased risk of adverse effects; pregnancy; breastfeeding; may interfere with thyroid-function tests; biguanides (withdraw 48 hours before administration; restart when renal function stabilized); important: because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available during radiographic procedures

Dosage:
Diagnostic radiography, ADULT and CHILD, route and dosage depend on procedure (consult manufacturer’s literature)

Administration.
Only by specialist radiographers, according to manufacturer’s directions

Adverse effects:
nausea, vomiting, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, cough, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension or hypertension; rarely, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, circulatory failure and cardiac arrest; occasionally anaphylactoid or hypersensitivity reactions; hyperthyroidism; pain on injection; extravasation may result in tissue damage, thrombophlebitis, thrombosis, venospasm and embolism
SECTION 15:
Disinfectants and antiseptics

15.1 Disinfectants and antiseptics
15.1 Disinfectants and antiseptics

ANTISEPTICS

An antiseptic is a type of disinfectant, which destroys or inhibits growth of micro-organisms on living tissues without causing injurious effects when applied to surfaces of the body or to exposed tissues. Some antiseptics are applied to the unbroken skin or mucous membranes, to burns and to open wounds to prevent sepsis by removing or excluding microbes from these areas. Iodine has been modified for use as an antiseptic. The iodophore, polyvidone-iodine, is effective against bacteria, fungi, viruses, protozoa, cysts and spores and significantly reduces surgical wound infections. The solution of polyvidone-iodine releases iodine on contact with the skin. Chlorhexidine has a wide spectrum of bactericidal and bacteriostatic activity and is effective against both Gram-positive and Gram-negative bacteria although it is less effective against some species of Pseudomonas and Proteus and relatively inactive against mycobacteria. It is not active against bacterial spores. Chlorhexidine is incompatible with soaps and other anionic materials, such as bicarbonates, chlorides, and phosphates, forming salts of low solubility which may precipitate out of solution. Ethanol has bactericidal activity and is used to disinfect skin prior to injection, venepuncture or surgical procedures. Cetrimide is a cationic and soap skin antiseptic. Hydrogen peroxide, is an oxidizer used for skin disinfection, particulary for cleaning and deodorising wounds and ulcers.

DISINFECTANTS

A disinfectant is a chemical agent, which destroys or inhibits growth of pathogenic micro-organisms in the non-sporing or vegetative state. Disinfectants do not necessarily kill all organisms but reduce them to a level, which does not harm health or the quality of perishable goods. Disinfectants are applied to inanimate objects and materials such as instruments and surfaces to control and prevent infection. They may also be used to disinfect skin and other tissues prior to surgery (see also Antiseptics, above).

Disinfection of water can be either physical or chemical. Physical methods include boiling, filtration and ultraviolet irradiation. Chemical methods include the addition of chlorine releasing compounds, such as sodium hypochlorite solution, chloramine T powder, or sodium dichloroisocyanurate (NaDCC) powder or tablets. Where water is not disinfected at source it may be disinfected by boiling or by chemical means for drinking, cleaning teeth and food preparation. Chlorine is a hazardous substance. It is highly corrosive in concentrated solution and splashes can cause burns and
damage the eyes. Appropriate precautions must be taken when concentrated chlorine solutions or powders are handled. The aldehyde bactericidal disinfectant, glutaral, is strongly active against both Gram-positive and Gram-negative bacteria. It is active against the tuberculosis bacillus, fungi such as Candida albicans, and viruses such as HIV and hepatitis B. A 2% w/v aqueous alkaline (buffered to pH 8) glutaral solution can be used to sterilize heat-sensitive pre-cleaned instruments and other equipment.

CHLORHEXIDINE GLUCONATE

Chlorhexidine gluconate is a representative disinfectant and antiseptic. Various agents can serve as alternatives Solution (Concentrate for solution), chlorhexidine gluconate 5%

Uses:
Antiseptic; disinfection of clean instruments

Precautions:
aqueous solutions—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); alcohol based solutions are flammable

Administration:
Antiseptic (pre-operative skin disinfection and hand washing), use 0.5% solution in alcohol (70%)
Antiseptic (wounds, burns and other skin damage), apply 0.05% aqueous solution
Disinfection of clean instruments, immerse for at least 30 minutes in 0.05% solution containing sodium nitrite 0.1% (to inhibit metal corrosion)
Emergency disinfection of clean instruments, immerse for 2 minutes in 0.5% solution in alcohol (70%)

DILUTION AND ADMINISTRATION.
According to manufacturer’s directions

Adverse effects:
Occasional skin sensitivity and irritation

HYDROGEN PEROXIDE

Solution, 3% and 6% gallon

Use
For skin disinfection, particularly to clean and deodorize wounds

Precaution
Large or deep wounds; avoid on healthy skin and eyes; bleaches fabric; incompatible with products containing iodine or potassium permanganate

CHLORINE RELEASING COMPOUNDS (EUSOL)

Chlorine releasing compounds are representative disinfectants. Various agents can serve as alternatives. *Powder for solution*, chlorine releasing compound, 1 g available chlorine/litre (1000 parts per million; 0.1%)

**Uses:**
Disinfection of surfaces, equipment, water

**Contraindications:**
Avoid exposure of product to flame; activity diminished in presence of organic material and increasing pH (can cause release of toxic chlorine gas)

**Administration:**
Surface disinfection (minor contamination), *apply* solutions containing 1000 parts per million
Instrument disinfection, *soak* in solution containing 1000 parts per million for a minimum of 15 minutes; to avoid corrosion do not soak for more than 30 minutes; rinse with sterile water

**DILUTION AND ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects:**
Irritation and burning sensation on skin

ETHANOL

Ethanol is a representative disinfectant. Various agents can serve as alternatives.

*Cutaneous solution*, ethanol 70%

**Uses:**
Disinfection of skin prior to injection, venepuncture or surgical procedures

**Precautions:**
Flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants

**Administration:**
Disinfection of skin, *apply* undiluted solution

**Adverse effects:**
Skin dryness and irritation with frequent application

CETRIMIDE

Solution, 20%

Use
Skin disinfection

Precaution
Avoid contact with eyes; avoid use in body cavities

Adverse Effects
Skin irritation and occasionally sensitisation

GLUTARALDEHYDE

Solution, glutaral 2% aqueous alkaline (pH 8) solution

Uses:
Disinfection and sterilization of instruments and surfaces

Precautions:
Minimize occupational exposure by adequate skin protection and measures to avoid inhalation of vapour

Administration:
Disinfection of clean instruments, *immerse* in undiluted solution for 10–20 minutes; up to 2 hours may be required for certain instruments (for example bronchoscopes with possible mycobacterial contamination); rinse with sterile water or alcohol after disinfection
Sterilization of clean instruments, *immerse* in undiluted solution for up to 10 hours; rinse with sterile water or alcohol after disinfection

Adverse effects:
(Occupational exposure) nausea, headache, airway obstruction, asthma, rhinitis, eye irritation and dermatitis and skin discoloration

POLYVIDONE-IODINE

Polyvidone-iodine is a representative antiseptic. Various agents can serve as alternatives

Cutaneous solution, polyvidone-iodine 10%

Uses:
antiseptic; skin disinfection

Contraindications:
Avoid regular or prolonged use in patients with thyroid disorders or those taking lithium; avoid regular use in neonates; avoid in very low birthweight infants

Precautions:
Pregnancy (Appendix 2); breastfeeding (Appendix 3); broken skin (see below); renal impairment (Appendix 4)

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, ADULT and CHILD
apply undiluted (see also Contraindications above)
Antiseptic (minor wounds and burns), ADULT and CHILD apply twice daily (see also Contraindications above)

Adverse effects:
Irritation of skin and mucous membranes; may interfere with thyroid function tests; systemic effects (see under Precautions)
Section 16: Diuretics

16.1 Thiazide diuretics
16.2 Loop diuretics
16.3 Potassium-sparing diuretics
16.4 Osmotic diuretics
16 Diuretics

Diuretics

Diuretics increase urinary excretion of water and electrolytes and are used to relieve oedema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure.

Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect.

Although **loop diuretics** are the most potent their duration of action is relatively short, whilst **thiazide diuretics** are moderately potent but produce diuresis for a longer period. **Potassium-sparing diuretics** are relatively weak. Carbonic anhydrase inhibitors are weak diuretics which are rarely used for their diuretic effect and are principally used to lower intraocular pressure in glaucoma (section 21.4.4).

**ELECTROLYTE IMBALANCE**

The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. **Hyponatraemia** is an adverse effect of all diuretics. The risk of **hypokalaemia**, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium-sparing diuretics can cause **hyperkalaemia**. Other electrolyte disturbances include **hypercalcaemia** (thiazides), **hypocalcaemia** (loop diuretics) and **hypomagnesaemia** (thiazide and loop diuretics).

Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, arrhythmias.

**ELDERLY**

The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the adult dose) and then adjusted carefully according to renal function, plasma electrolytes and diuretic response.

16.1 **Thiazide diuretics**

Thiazide diuretics, such as **hydrochlorothiazide**, are mod-

erately potent and act by inhibiting sodium and chloride reab-
sorption at the beginning of the distal convoluted tubule. They
produce diuresis within 1–2 hours of oral administration and
most have a duration of action of 12–24 hours.
Thiazide diuretics are used in the management of oedema as-
associated with mild to moderate congestive heart failure, renal
dysfunction or hepatic disease; however, thiazides are not ef-
fective in patients with poor renal function (creatinine clearance
of less than 30 ml per minute). In severe fluid retention a loop
diuretic may be necessary.

In hypertension, a thiazide diuretic is used at a low dose to
lower blood pressure with very little biochemical disturbance;
the maximum therapeutic effect may not be seen for several
weeks. Higher doses should not be used because they do
not necessarily increase the hypotensive response but may
cause marked changes in plasma potassium, magnesium,
uric acid, glucose and lipids. If a thiazide alone does not lower
blood pressure adequately, it may be used in combination
with another antihypertensive such as a beta-adrenoceptor
antagonist (section 12.3).

Urinary excretion of calcium is reduced by thiazide diuretics
and this property is occasionally utilized in the treatment of
idiopathic hypercalciuria in patients with calcium-containing
calculi. Paradoxically, thiazide diuretics are used in the treat-
ment of diabetes insipidus, since in this disease they reduce
urine volume.

Thiazide diuretics, especially in high doses, produce a marked
increase in potassium excretion which may cause hypokalaem-
ia; this is dangerous in patients with severe coronary artery
disease and those being treated with cardiac glycosides. In
hepatic failure hypokalaemia can precipitate encephalopathy,
particularly in alcoholic cirrhosis. Potassium-sparing diuretics
are used as a more effective alternative to potassium supple-
ments for prevention of hypokalaemia induced by thiazide
diuretics; however supplementation with potassium in any form
is seldom necessary with the smaller doses of diuretics used
to treat hypertension.

HYDROCHLOROTHIAZIDE

Hydrochlorothiazide is a representative thiazide diuretic. Vari-
ous drugs can serve as alternatives

Tablets, hydrochlorothiazide, 25 mg, 50 mg

Uses:
oedema; diabetes insipidus; hypertension (see also section
12.3); heart failure (section 12.4)

Contraindications:
severe renal or severe hepatic impairment; hyponatraemia,
hypercalcaemia, refractory hypokalaemia, symptomatic hype-
ruricaemia; Addison disease

**Precautions:**
renal (Appendix 4), hepatic impairment (Appendix 5); pregnancy (Appendix 2), breastfeeding (Appendix 3); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; **interactions:** Appendix 1

**Dosage:**
Hypertension, *by mouth*, **ADULT** 12.5–25 mg daily; **ELDERLY** initially 12.5 mg daily

Oedema, *by mouth*, **ADULT** initially 25 mg daily on rising, increasing to 50 mg daily if necessary; **ELDERLY** initially 12.5 mg daily

Severe oedema in patients unable to tolerate loop diuretics, *by mouth*, **ADULT** up to 100 mg *either* daily *or* on alternate days (maximum 100 mg daily)

Nephrogenic diabetes insipidus, *by mouth*, **ADULT** initially up to 100 mg daily

**Adverse effects:**
hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraeemic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes); hypercalcaemia; hyperglycaemia; hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible), blood disorders (including neutropenia, thrombocytopenia); pancreatitis, intrahepatic cholestasis and hypersensitivity reactions (including pneumonitis, pulmonary oedema, severe skin reactions) also reported; acute renal failure

### 16.2 Loop diuretics

Loop diuretics, or high-ceiling diuretics, such as *furosemide*, are the most potent and rapidly produce an intense dose-dependent diuresis of relatively short duration. Oral furosemide produces diuresis within 30–60 minutes of administration, with the maximum diuretic effect in 1–2 hours. The diuretic action lasts for 4–6 hours. Intravenous furosemide produces diuresis within 5 minutes, with the maximum diuretic effect in 20–60 minutes and diuresis complete within 2 hours. *Bumetanide*, has similar activity to furosemide, both acting within an hour of oral administration and diuresis is complete within 6 hours so that if necessary, they can be given twice in one day without interfering with sleep.

Loop diuretics inhibit reabsorption from the ascending loop of Henlé in the renal tubule and are useful, particularly in situations where rapid and effective diuresis is needed such as reduction of acute pulmonary oedema due to left ventricular failure. They are also used to treat oedema associated with...
renal and hepatic disorders and are used in high doses in the management of oliguria due to chronic renal insufficiency. Loop diuretics may be effective in patients unresponsive to thiazide diuretics. Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics than with thiazide diuretics; if required, potassium-sparing diuretics may be used for prevention of hypokalaemia. Loop diuretics may cause hypovolaemia and excessive use can produce severe dehydration with the possibility of circulatory collapse. Furosemide may cause hyperuricaemia and precipitate attacks of gout. Rapid high-dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

**FUROSEMIDE**

Furosemide is a representative loop diuretic. Various drugs can serve as alternatives

*Tablets,* furosemide 40 mg

*Injection* (Solution for injection), furosemide 10 mg/ml, 2-ml ampoule

**Uses:**
Oedema; oliguria due to renal failure

**Contraindications:**
Renal failure with anuria; precomatose states associated with liver cirrhosis

**Precautions:**
monitor electrolytes particularly potassium and sodium; hypotension; elderly (reduce dose); pregnancy (Appendix 2), breastfeeding (Appendix 3); correct hypovolaemia before using in oliguria; renal impairment (Appendix 4), hepatic impairment (Appendix 5); prostatic enlargement; porphyria;

**Interactions:**
Appendix 1

**Dosage:**

- **Oedema,** by mouth, **ADULT** initially 40 mg daily on rising; maintenance, 20–40 mg daily; may be increased to 80 mg daily or more in resistant oedema; **CHILD** 1–3 mg/kg daily (maximum 40 mg daily)

- **Acute pulmonary oedema,** by slow intravenous injection, **ADULT** 20–50 mg, if necessary increase by 20-mg steps every 2 hours; if effective single dose is more than 50 mg, consider using slow intravenous infusion at a rate not exceeding 4 mg/minute; **CHILD** 0.5–1.5 mg/kg daily (maximum 20 mg daily)

- **Oliguria** (glomerular filtration rate less than 20 ml/minute), by slow intravenous infusion at a rate not exceeding 4 mg/minute, **ADULT** initially 250 mg over 1 hour; if urine output not satisfactory during hour after first dose, infuse 500 mg over 2 hours then, if no satisfactory response during hour after second dose, infuse 1 g over 4 hours; if no response after third dose,
dialysis probably necessary

**NOTE.**

Dose to be diluted in suitable amount of infusion fluid, depending on hydration of patient

**Adverse effects:**

hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraeic alkalosis (for symptoms of fluid and electrolyte imbalance, see introductory notes), increased calcium excretion, hypovolaemia, hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia and gout; rarely rash, photosensitivity, bone marrow depression (withdraw treatment), pancreatitis (with large parenteral doses), tinnitus and deafness (with rapid administration of large parenteral doses and in renal impairment; deafness may be permanent if other ototoxic drugs taken)

**BUMETANIDE**

Tablet, 1mg

**Use**

Oedema, oliguria due to renal failure

**Adverse Effects**

See under furosemide; also myalgia

**Precaution**

See under furosemide

**Contraindications**

See under furosemide

**Dose**

*By mouth*, 1mg in the morning, repeated after 6-8 hours if necessary; severe cases increase up to 5mg or more daily

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16.3 Potassium-sparing diuretics

Potassium-sparing diuretics include *spironolactone*; this is a weak diuretics and reduce potassium excretion and increase sodium excretion in the distal tubule. Spironolactone, which acts by antagonising aldosterone, has a relatively slow onset of action requiring 2–3 days to achieve maximum diuretic effect, and a similar period of 2–3 days for diuresis to cease after discontinuation of treatment. Spironolactone is used in the treatment of refractory oedema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from hypokalaemia. A low dose of spironolactone is beneficial in severe heart failure in patients who are already taking an ACE inhibitor and a
diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of hypokalaemia and of hypertension. The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is hyperkalaemia, which can be life-threatening. These diuretics are thus best avoided or used very carefully in patients who have or may develop hyperkalaemia, such as those with renal failure, patients receiving other potassium-sparing diuretics and patients taking ACE inhibitors or potassium supplements.

**SPIRONOLACTONE**

*Tablets,* spironolactone, 25 mg  
**Uses:** refractory oedema in congestive heart failure; adjunct to ACE inhibitor and diuretic in severe congestive heart failure; nephrotic syndrome; hepatic cirrhosis with ascites and oedema; ascites associated with malignancy; primary hyperaldosteronism  
**Contraindications:** pregnancy (Appendix 2); breastfeeding; hyperkalaemia; hyponatraemia; severe renal impairment; Addison disease  
**Precautions:** monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalaemia); elderly (reduce dose); diabetes mellitus; renal impairment (Appendix 4); hepatic impairment; porphyria; high doses carcinogenic in rodents; **interactions:** Appendix 1  
**Dosage:** Oedema, *by mouth,* ADULT 100–200 mg daily, increased if necessary to 400 mg daily in resistant oedema; usual maintenance dose 75–200 mg daily; CHILD initially 3 mg/kg daily in divided doses  
Primary hyperaldosteronism, *by mouth,* ADULT, diagnosis, 400 mg daily for 3–4 weeks (see notes above); preoperative management, 100–400 mg daily; if not suitable for surgery, lowest effective dose for long-term maintenance  
Adjunct in severe heart failure, *by mouth,* ADULT usually 25 mg daily  
**Adverse effects:** hyperkalaemia, hyponatraemia, hyperchloraemic acidosis, dehydration (for symptoms of fluid and electrolyte imbalance see introductory notes); transient increase in blood urea nitrogen; diarrhoea; gynaecomastia, menstrual irregularities; impotence, hirsutism, deepening of voice; rash, ataxia, fever, hepatotoxicity

16.4 Osmotic diuretics

Osmotic diuretics, such as mannitol, are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. Osmotic diuretics are used to reduce or prevent cerebral oedema, to reduce raised intraocular pressure or to treat disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma. Reduction of cerebrospinal and intraocular fluid pressure occurs within 15 minutes of the start of infusion and lasts for 3–8 hours after the infusion has been discontinued; diuresis occurs after 1–3 hours.

Circulatory overload due to expansion of extracellular fluid is a serious adverse effect of mannitol; as a consequence, pulmonary oedema can be precipitated in patients with diminished cardiac reserve, and acute water intoxication may occur in patients with inadequate urine flow.

**MANNITOL**

*Infusion* (Solution for infusion), mannitol, 20%

**Uses:**
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

**Dosage:**
Test dose if patient oliguric or renal function is inadequate, *by intravenous infusion*, as a 20% solution, 200 mg/kg body weight infused over 3–5 minutes; repeat test dose if urine output less than 30–50 ml/hour; if response inadequate after second test dose, re-evaluate patient

Raised intracranial or intraocular pressure, *by intravenous infusion*, as a 20% solution infused over 30–60 minutes, 0.25–2 g/kg body weight

Cerebral oedema, *by intravenous infusion*, as a 20% solution infused rapidly, 1 g/kg body weight

**PHARMACEUTICAL PRECAUTIONS.**

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.
Adverse effects:
fluid and electrolyte imbalance (for symptoms see introductory notes); circulatory overload, acidosis; pulmonary oedema particularly in diminished cardiac reserve; chills, fever, chest pain, dizziness, visual disturbances; hypertension; urticaria, hypersensitivity reactions; extravasation may cause oedema, skin necrosis, thrombophlebitis; rarely, acute renal failure (large doses)
SECTION 17: GASTROINTESTINAL DRUGS

17.1 Antacids and other antiulcer medicines
17.2 Antiemetic medications
17.3 Antihaemorrhoidal medicines
17.4 Anti-inflammatory medicines
17.5 Antispasmodic medicines
17.6 Laxitives
17.7.1 Oral Rehydration
17.2.2 Antidiarrhoeal (symptomatic) medicines
Antacids and other antiulcer drugs

Antacids (usually containing aluminium or magnesium compounds) can often relieve symptoms in ulcer dyspepsia and in non-erosive gastro-oesophageal reflux; they are also sometimes used in non-ulcer dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, 4 or more times daily; additional doses may be required up to once an hour. Conventional doses for example 10 ml 3 or 4 times daily of liquid magnesium–aluminium antacids promote ulcer healing, but less well than antisecretory drugs (such as an H₂-receptor antagonist); proof of a relationship between healing and neutralizing capacity is lacking. Liquid preparations are more effective than solids. 

Aluminium- and magnesium-containing antacids (for example aluminium hydroxide, and magnesium hydroxide), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable antacids for most purposes. Magnesium-containing antacids have a laxative effect whereas aluminium-containing antacids may be constipating. H₂-receptor antagonists heal gastric and duodenal ulcers by reducing the secretion of gastric acid as a result of histamine H₂-receptor blockade; they can also relieve gastro-oesophageal reflux disease. High doses of H₂-receptor antagonists have been used in the Zollinger–Ellison syndrome, but a proton-pump inhibitor is now preferred. Maintenance treatment with low doses has largely been replaced in Helicobacter pylori positive patients by eradication regimens (see below). Maintenance treatment may occasionally be used for those with frequent severe recurrences and for the elderly who suffer ulcer complications.

TREATMENT OF UNDIAGNOSED DYSPEPSIA WITH H₂-RECEPTOR ANTAGONISTS MAY BE ACCEPTABLE IN YOUNGER PATIENTS BUT CARE IS REQUIRED IN OLDER PEOPLE BECAUSE THEIR SYMPTOMS MAY BE CAUSED BY GASTRIC CANCER.

PEPTIC ULCER

Ulcer disease is caused by peptic ulceration that involves the stomach, duodenum, and lower oesophagus. General and inexpensive measures like introducing healthy life-style, stopping smoking and taking antacids should be promoted. The possibility of malignant disease should be considered.
in all patients over the age of 40 years who are suspected of having an ulcer.

Gastric and duodenal ulcers are healed by 4–8 weeks treatment with $H_2$-receptor antagonists but there is a high rate of relapse (greater than 70% over 2 years) requiring maintenance therapy. Relapses can be prevented very successfully by eradicating *Helicobacter pylori* which is causally associated with most peptic ulcers (except those related to NSAID use). Eradication of *H. pylori* reduces the relapse rate to about 4–8%. This is undoubtedly cost-effective compared to the alternatives of long-term maintenance therapy with low-dose $H_2$-receptor antagonists or repeated treatment of recurrent ulcers. It is recommended that the presence of *H. pylori* is confirmed before starting eradication treatment, particularly for gastric ulcers. The urea breath test is used widely to test for *H. pylori*, but it may produce false negative results if used soon after proton pump inhibitors or antibacterials. Eradication regimens are based on a combination of an acid-reducing (‘antisecretory’) drug and antibiotics.

The following model eradication regimen is suggested on the basis of its efficacy and simplicity (only doses suitable for adults are shown):

- **omeprazole** 40 mg daily for 1 week
  - plus
- **metronidazole** 400 mg three times daily for 1 week
  - plus
- **amoxicillin** 500 mg three times daily for 1 week

The decision on choosing an eradication regimen for a particular country should take into account local resistance to antibacterials, cost and availability of the necessary drugs.

**NSAID-ASSOCIATED ULCERS**

Gastrointestinal bleeding and ulceration may occur with NSAID use. To avoid this, emphasis should be on stopping NSAID use but this is not always possible. A proton pump inhibitor may be considered for protection against NSAID-associated gastric and duodenal ulcers. An $H_2$-receptor antagonist may be effective for protection against NSAID-associated duodenal ulcers only.

Patients who must continue NSAID therapy after ulcer development may take high-dose $H_2$-receptor antagonists concomitantly, but ulcers tend to heal more slowly with $H_2$-receptor antagonists if NSAIDs are continued. A proton-pump inhibitor such as omeprazole is more effective but it is also more expensive.

In patients who can discontinue NSAID therapy after ulcer development, treatment with an $H_2$-receptor antagonist is effective, but a treatment period of up to 8 weeks may be necessary. A proton pump inhibitor usually produces the most rapid healing.

After healing, continued prophylaxis is required.

**DYSPEPSIA**

Dyspepsia covers pain, fullness, early satiety, bloating, or nausea. It can occur with gastric and duodenal ulceration and gastric cancer but most commonly it is of uncertain origin. Patients with non-ulcer dyspepsia should be advised to avoid smoking, alcohol and aggravating foods, and to eat small regular meals to aid digestion. Non-ulcer dyspepsia tends to be self-limiting but antacids and H$_2$-receptor antagonists are often used to suppress gastric acid. Effective treatment is important in the presence of severe oesophageal ulceration to prevent longer term complications such as oesophageal stricture and carcinoma.

**GASTRO-OESOPHAGEAL REFLUX DISEASE**

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

The management of gastro-oesophageal reflux disease includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms and treatment is then adjusted according to response. For mild symptoms of gastro-oesophageal reflux disease, initial management may include the use of antacids. H$_2$-receptor antagonists suppress acid secretion and they may relieve symptoms and permit reduction in antacid consumption. Severe symptoms initially require a short-course of a proton-pump inhibitor.

**ZOLLINGER–ELLISON SYNDROME**

Management of Zollinger–Ellison syndrome requires high dose H$_2$-receptor antagonist treatment. The proton pump inhibitors are more effective particularly for cases resistant to other treatment but they are more expensive.

**ALUMINIUM HYDROXIDE**

- **Tablets**, aluminium hydroxide 500 mg
- **Oral suspension**, aluminium hydroxide 320 mg/5 ml

**Uses:**
- ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux; hyperphosphataemia

**Contraindications:**
- hypophosphataemia; undiagnosed gastrointestinal or rectal bleeding; appendicitis; porphyria

Precautions:
impaired renal function and renal dialysis (Appendix 4); hepatic
impairment (Appendix 5); constipation; dehydration; fluid re-
striction; gastrointestinal disorders associated with decreased
bowel motility or obstruction; interactions: Appendix 1
Dosage:
Dyspepsia, gastro-oesophageal reflux, by mouth, ADULT 1–2
tablets chewed 4 times daily and at bedtime or 5–10 ml suspen-
sion 4 times daily between meals and at bedtime; CHILD 6–12
years 5 ml up to three times daily
Hyperphosphataemia, by mouth, ADULT 2–10 g daily in divided
doses with meals
Patient Advice.
Do not take other medicines within 2–4 hours of aluminium
hydroxide preparations. May be taken with water to reduce
constipating adverse effects
Adverse effects:
constipation; intestinal obstruction (large doses); hypophospha-
taemia with increased bone resorption, hypercalciuria and risk
of osteomalacia (patients on low phosphate diet or prolonged
therapy); hyperaluminaemia—resulting in osteomalacia,
encephalopathy, dementia, microcytic anaemia (in chronic
renal failure treated with aluminium hydroxide as phosphate-
binding agent)

MAGNESIUM HYDROXIDE

Oral suspension, magnesium hydroxide equivalent to magne-
sium oxide 550 mg/10 ml
Uses:
ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux
Contraindications:
severe renal impairment
Precautions:
renal impairment (Appendix 4); hepatic impairment (Appendix
5); interactions: Appendix 1
Dosage:
Dyspepsia, gastro-oesophageal reflux, by mouth, ADULT 5–10
ml repeated according to patient’s needs
Adverse effects:
diarrhoea; in renal impairment—hypermagnesaemia resulting
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
Aluminium/Magnesium Hydroxide
Tablet, 300 mg
Suspension, 320 mg/5ml
Dose:

Tablet, 1-2 tablets chewed 3-4 times daily
Suspension, 10-20 ml 3 times daily, 20-60 minutes after meals and at bed time or when required. CHILD under 12 years not recommended

RANITIDINE

Ranitidine is a representative H₂-receptor antagonist. Various drugs can serve as alternatives
Tablets, ranitidine (as hydrochloride) 150 mg
Oral solution, ranitidine (as hydrochloride) 75 mg/5 ml
Injection (Solution for injection), ranitidine (as hydrochloride) 25 mg/ml, 2-ml ampoule

Uses:
benign gastric and duodenal ulceration, gastro-oesophageal reflux, Zollinger–Ellison syndrome, other conditions where gastric acid reduction is beneficial

Contraindications:
porphyria

Precautions:
hepatic impairment (Appendix 5); renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3); middle-aged or older patients and those whose symptoms change—may mask gastric cancer; interactions: Appendix 1

Dosage:
Benign gastric and duodenal ulceration, by mouth, adult 150 mg twice daily or 300 mg at night for 4–8 weeks, up to 6 weeks in chronic episodic dyspepsia, and up to 8 weeks in NSAID-associated ulceration (in duodenal ulcer 300 mg can be given twice daily for 4 weeks to achieve a higher healing rate); maintenance, 150 mg at night; CHILD (peptic ulcer) 2–4 mg/kg twice daily, maximum 300 mg daily
Benign gastric and duodenal ulceration, reflux oesophagitis, Zollinger–Ellison syndrome, by intramuscular injection, adult 50 mg every 6–8 hours or by slow intravenous injection, 50 mg diluted to 20 ml and given over at least 2 minutes, may be repeated every 6–8 hours or by intravenous infusion, 25 mg/hour for 2 hours, may be repeated every 6–8 hours
Duodenal ulceration associated with H. pylori, see notes above
Prophylaxis of NSAID-induced duodenal ulcer, by mouth, adult 150 mg twice daily
Reflux oesophagitis, by mouth, adult 150 mg twice daily or 300 mg at night for up to 8 weeks, or if necessary 12 weeks (moderate to severe, 150 mg 4 times daily for up to 12 weeks); long-term treatment of healed oesophagitis, 150 mg twice daily
Zollinger–Ellison syndrome, by mouth, adult 150 mg 3 times
daily; up to 6 g daily in divided doses has been used
Gastric acid reduction (prophylaxis of acid aspiration) in
obstetrics, by mouth, adult 150 mg at onset of labour, then
every 6 hours; surgical procedures, by intramuscular or slow
intravenous injection, adult 50 mg 45–60 minutes before incul-
tion of anaesthesia (intravenous injection diluted to 20 ml and
given over at least 2 minutes), or by mouth, 150 mg 2 hours
before induction of anaesthesia, and also, when possible on
the preceding evening
Prophylaxis of stress ulceration, adult initial slow intravenous
injection of 50 mg diluted to 20 ml and given over at least 2
minutes then by continuous intravenous infusion, 125–250
micrograms/kg per hour (may be followed by 150 mg twice
daily by mouth when oral feeding commences)

Adverse effects:
diarrhoea and other gastrointestinal disturbances, headache,
dizziness, rash, tiredness, acute pancreatitis, bradycardia, AV
block, confusion, depression; rarely hallucinations (particu-
larly in the elderly or the very ill), hypersensitivity reactions
(including fever, arthralgia, myalgia, anaphylaxis), blood dis-
orders (including agranulocytosis, leukopenia, pancytopenia,
thrombocytopenia), hepatitis, tachycardia, agitation, visual
disturbances, erythema multiforme, alopecia, gynaecomastia
and impotence

OMEPRAZOLE

Tablet, omeprazole 20mg
Injection, powder for reconstitution, omeprazole (assodium
salt) 40–mg vial

Uses:
benign gastric and duodenal ulceration, gastro-oesophageal
reflux, Zollinger–Ellison syndrome, other conditions where
gastric acid reduction is beneficial

Cautions:
use with caution in patients with liver disease, in pregnancy,
and in breast-feeding. Proton pump inhibitors may mask
symptoms of gastric cancer; particular care is required in
those presenting with “alarm features”, in such cases gastric
malignancy should be ruled out before treatment

Dosage:
by mouth, beingn gastric and duodenal ulcers, 20 mg once
daily for 4 weeks in duodenal ulceration or 8 weeks in gastric
ulceration; in severe or recurrent cases increase to 40 mg daily;
maintenance for recurrent duodenal ulcer, 20 mg once daily;
prevention of relapse in duodenal ulcer, 10 mg daily increasing
to 20 mg once daily if symptoms return
NSAID-associated duodenal or gastric ulcer and gastroduo-
denal erosions, 20 mg once daily for 4 weeks, continued for
further 4 weeks if not fully healed; prophylaxis in patients with a history of NSAID-associated duodenal or gastric ulcers, gastroduodenal lesions, or dyspeptic symptoms who require continued NSAID treatment, 20 mg once daily
Zollinger-Ellison syndrome, initially 60 mg once daily; usual range 20-120 mg daily (above 80 mg in 2 divided doses)
Gastric acid reduction during general anaesthesia (prophylaxis of aspiration), 40 mg on the preceding evening then 40 mg 2-6 hours before surgery
Gastro-oesophageal reflux disease, 20 mg once daily for 4 weeks, continued for further 4-8 weeks if not fully healed; 40 mg once daily has been given for 8 weeks in gastro-oesophageal reflux disease refractory to other treatment, maintenance 20 mg once daily
Acid reflux disease (long-term management), 10 mg daily increasing to 20 mg once daily if symptoms return
Acid-related dyspepsia, 10-20 mg once daily for 2-4 weeks according to response
CHILD over 2 years, severe ulcerating reflux oesophagitis. 0.7-1.4 mg /kg daily for 4-12 weeks max. 40 mg daily (to be initiated by hospital paediatrician)
By intravenous injection over 5 minutes or by intravenous infusion, prophylaxis of acid aspiration, 40 mg completed 1 hour before surgery
Benign gastric ulcer, duodenal ulcer and gastro-oesophageal reflux, 40 mg once daily until oral administration possible; CHILD not recommended

**Adverse effects:**
- gastrointestinal disturbances (including nausea, vomiting, abdominal pain, flatulence, diarrhoea, constipation), headache, and dizziness. Less frequent side-effects include dry mouth, insomnia, drowsiness, malaise, blurred vision. Also reported, paraesthesia, vertigo, alopecia, gynaecomastia

17.2 Antiemetic drugs

**Metoclopramide** has antiemetic properties and also stimulates upper gastrointestinal motility. Metoclopramide is effective against nausea and vomiting associated with gastrointestinal disorders or migraine, following surgery and chemotherapy and is also effective against radiation-induced nausea and vomiting. Combining metoclopramide with corticosteroids (such as dexamethasone) can improve its antiemetic effect in chemotherapy-induced nausea and vomiting. Metoclopramide may be useful in the management of gastro-oesophageal reflux and gastroparesis, as well as preoperatively in the prevention of aspiration syndromes. It is also used to facilitate intubation of the small bowel during radiographic examinations. Metoclopramide is not effective in the prevention or treatment of motion sickness.

Metoclopramide may cause acute dystonic reactions with facial and skeletal muscle spasms and oculogyric crises. These reactions are most common in the young (especially girls and young women) and the elderly; they occur shortly after the start of treatment and subside within 24 hours of drug withdrawal. **Promethazine** is a phenothiazine that in addition to D2 dopaminergic blockade has pronounced histamine H₁ and muscarinic receptor blocking properties. It is effective in the prevention and treatment of vertigo and motion sickness. Promethazine may be useful in the prevention and treatment of postoperative and drug-induced nausea and vomiting. It has limited effect on chemotherapy-induced mild to moderate emesis. **Dimenhydrinate**, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and significant sedative effects. It is used mainly as an antiemetic in the prevention and treatment of motion sickness. It is also used for the symptomatic treatment of nausea and vertigo caused by Meniere’s disease and other vestibular disturbances.

**Metoclopramide hydrochloride**

*Tablets*, metoclopramide hydrochloride 10 mg  
*Injection* (Solution for injection), metoclopramide hydrochloride 5 mg/ml, 2-ml ampoule  
**Uses:**  
nausea and vomiting in gastrointestinal disorders and treatment with cytotoxics (section 8.2) or radiotherapy; gastro-oesophageal reflux; gastroparesis; premedication and postoperatively;  
aid to gastrointestinal intubation; nausea and vomiting in migraine (section 7.1)

**Note.**  
In children (and in some countries, patients under 20 years) use restricted to severe intractable vomiting of known cause, vomiting of radiotherapy and chemotherapy, aid to gastrointestinal intubation, premedication  
**Contraindications:**  
gastrointestinal obstruction, haemorrhage or perforation; 3–4 days after gastrointestinal surgery; convulsive disorders; phaeochromocytoma  
**Precautions:**  
elderly, children and young adults; hepatic impairment (Appendix 5); renal impairment (Appendix 4); may mask underlying disorders such as cerebral irritation; avoid for 3–4 days after gastrointestinal surgery; pregnancy (Appendix 2); breastfeeding (Appendix 3); Parkinson disease; epilepsy; depression; porphyria; **interactions:** Appendix 1  
**Dosage:**

Nausea and vomiting, gastro-oesophageal reflux, gastroparesis, by mouth or by intramuscular injection or by slow intravenous injection (over 1–2 minutes), ADULT 10 mg 3 times daily; young ADULT 15–19 years (under 60 kg) 5 mg 3 times daily; CHILD up to 1 year (up to 10 kg) 1 mg twice daily, 1–3 years (10–14 kg) 1 mg 2–3 times daily, 3–5 years (15–19 kg) 2 mg 2–3 times daily, 5–9 years (20–29 kg) 2.5 mg 3 times daily, 9–14 years (30 kg and over) 5 mg 3 times daily (usual maximum 500 micrograms/kg daily, particularly for children and young adults)

Premedication, by slow intravenous injection, ADULT 10 mg as a single dose

Aid to gastrointestinal intubation, by mouth or by intramuscular injection or by slow intravenous injection, ADULT 10–20 mg as a single dose 5–10 minutes before examination; young ADULT (15–19 years), 10 mg; CHILD under 3 years 1 mg, 3–5 years 2 mg, 5–9 years 2.5 mg, 9–14 years 5 mg

Note.

High dose metoclopramide with cytotoxic chemotherapy, see section 8.2

Adverse effects: extrapyramidal symptoms (especially in children and young adults; see notes above); tardive dyskinesias on prolonged use; hyperprolactinaemia; drowsiness, restlessness, dizziness, headache, diarrhoea, depression, hypotension and hypertension reported; rarely, neuroleptic malignant syndrome; rashes, pruritus, oedema; cardiac conduction abnormalities following intravenous administration; rarely methaemoglobinemia (more severe in G6PD deficiency)

PROMETHAZINE HYDROCHLORIDE

Tablets, promethazine hydrochloride 10 mg, 25 mg
Elixir (Oral solution), promethazine hydrochloride 5 mg/5 ml
Injection (Solution for injection), promethazine hydrochloride 25 mg/ml, 2-ml ampoule

Uses: nausea, vomiting, labyrinthine disorders, motion sickness; premedication (section 1.3)

Contraindications: porphyria

Precautions: prostatic hypertrophy; urinary retention; glaucoma; hepatic disease (Appendix 5); epilepsy; elderly and children (more susceptible to adverse effects); pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

PatientAdvice
May impair ability to perform skilled tasks, for example operating machinery, driving
Dosage:
Nausea and vomiting (including postoperative), by mouth or by intramuscular injection or by slow intravenous injection (diluted to 2.5 mg/ml in water for injection), **ADULT** 12.5–25 mg, repeated at intervals of not less than 4 hours (usual maximum, 100 mg in 24 hours)
Motion sickness, prevention, by mouth, **ADULT** 20–25 mg at bedtime on night before travel, repeated on day of travel if necessary; **CHILD** 2–5 years, 5 mg at night and on day of travel, if necessary; 5–10 years, 10 mg at night and on day of travel, if necessary

Dilution and administration.
Intravenous injection, according to manufacturer’s directions

Adverse effects:
drowsiness, dizziness, sedation (but paradoxical stimulation may occur, especially with high doses or in children and elderly); headache, psychomotor impairment; urinary retention, dry mouth, blurred vision, gastrointestinal disturbances; hypersensitivity reactions; rashes, photosensitivity reactions; jaundice; blood disorders; cardiovascular adverse effects—after injection; venous thrombosis at site of intravenous injection; pain on intramuscular injection

**Dimenhydrinate Tablet, 50 mg**

Uses:
prophylaxis of nausea, vomiting, dizziness associated with motion sickness

Contraindications:
see under promethazine

Cautions:
see under promethazine

Dosage:
usual dose by mouth is 50-100 mg given 3-4 times daily. For the prevention of motion sickness, the first dose should be taken at least 30 minutes before traveling. Typical doses for children are: 2 up to 6 years. 12.5-25 mg every 6-8 hours to a maximum of 75 mg daily (in some countries lower doses of 6.25-12.5 mg are given two or three times daily); 6 to 12 years, 25-50 mg every 6 to 8 hours (again lower doses are used in some countries)

Dimenhydramine may be given parenterally in usual doses of 50 mg, a concentration of 5% being used for intramuscular injection and 0.5% for slow intravenous injection (usually over 2 minutes). Children have been given dimenhydramine by intramuscular or slow intravenous injection in a dose of 1.25 mg/kg body-weight 4 times daily to a maximum of 300 mg daily

Adverse effects:
see under promethazine

17.3 Antihaemorrhoidal drugs

Haemorrhoids are enlarged or varicose veins of the tissues at the anus or rectal outlet. They are the most frequent cause of rectal bleeding. Anal and perianal pruritus, soreness and excoriation occur commonly in patients suffering from haemorrhoids, fistulas and proctitis. Careful local toilet with attention to any minor faecal soiling, adjustment of the diet to avoid hard stools, the use of bulk-forming materials such as bran and a high residue diet are helpful.

Soothing preparations containing mild astringents such as bismuth subgallate, zinc oxide and hamamelis with lubricants, vasoconstrictors or mild antiseptics, in the form of topical ointments, creams and suppositories, are used to provide symptomatic relief. Local anaesthetics are included in some preparations to relieve pain. Corticosteroids may be combined in such preparations (but should only be used after exclusion of infection); they are suitable for occasional short-term use, but prolonged use can cause atrophy of the anal skin.

**LOCAL ANAESTHETIC, ASTRINGENT AND ANTI-INFLAMMATORY DRUG**

*Ointment or suppository*

**Uses:**
short-term symptomatic treatment of hemorrhoids

**ANUSOL**

*Suppository*, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 10 mg, Peru balsam 49 mg, zinc oxide 296 mg

**Dose:**
insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days, CHILD not recommended

**XYLOPROCT**

*Ointment*, aluminium acetate 3.5%, hydrocortisone acetate 0.27%, lidocaine 5%, zinc oxide 18%

**Dose:**
apply several times daily; short-term use only

**17.4 Anti-inflammatory drugs**

Ulcerative colitis and Crohn disease are inflammatory diseases of the intestinal tract.

**ULCERATIVE COLITIS**

Acute attacks of ulcerative colitis require treatment with local...
corticosteroids such as hydrocortisone in the form of suppositories or retention enemas. Because of the risk of intestinal perforation, rectal administration of hydrocortisone must be used with extreme caution in patients with severe ulcerative disease and should not be given to such patients without conducting a thorough proctological examination. More extensive disease requires oral corticosteroid treatment and severe extensive or fulminant disease needs hospital admission and intravenous corticosteroid administration; other therapy may include intravenous fluid and electrolyte replacement, blood transfusion, and possibly parenteral nutrition and antibiotics.

The aminosalicylate sulfasalazine is useful in the treatment of symptomatic disease. It also has value in the maintenance of remission in ulcerative colitis for which corticosteroid treatment is unsuitable because of adverse effects. In resistant or frequently relapsing cases azathioprine 2–2.5 mg/kg daily (section 8.1) given under close supervision may be helpful. Laxatives are required to facilitate bowel movement when proctitis is present. Antimotility drugs such as codeine and antispasmodic drugs should not be used in active ulcerative colitis because they can precipitate paralytic ileus and megacolon. Diarrhoea resulting from reduced bile salt absorption may improve with colestyramine. General nutritional care and appropriate supplements are essential. High-fibre or low-residue diets should be used as appropriate. Irritable bowel syndrome during remission of ulcerative colitis requires avoidance of a high-fibre diet and possibly treatment with an antispasmodic (see section 17.5).

CROHN DISEASE

Treatment of Crohn disease of the colon is similar to that of ulcerative colitis. In small bowel disease sulfasalazine may have marginal benefit. Symptoms and inflammation associated with disease exacerbation are suppressed by oral corticosteroids such as prednisolone. Metronidazole may be beneficial in the treatment of active Crohn disease particularly with perianal involvement, possibly through its antibacterial activity. Other antibacterials should be given if specifically indicated (for example, sepsis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel. General nutritional care and appropriate supplements are essential.

HYDROCORTISONE

Hydrocortisone retention enema is a representative rectal corticosteroid preparation (other than suppository). Various formulations can serve as alternatives

Hydrocortisone rectal preparations are complementary drugs
Suppositories, hydrocortisone acetate 25 mg
Retention enema (Rectal solution), hydrocortisone 100 mg, 60-ml bottle

Uses:
ulcerative colitis, proctitis, proctosigmoiditis; anaphylaxis (section 3.1); skin (section 13.3); adrenocortical insufficiency (section 18.1)

Contraindications:
use of enemas in bowel obstruction, bowel perforation, or extensive fistulas; untreated infections

Precautions:
proctological examination required before treatment; systemic absorption may occur (see section 18.1); prolonged use should be avoided; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Ulcerative colitis, proctitis, by rectum (suppositories), ADULT 25 mg twice daily for 2 weeks; may be increased to 25 mg 3 times daily or 50 mg twice daily in severe cases; in factitial proctitis treatment may be required for 6–8 weeks
Ulcerative colitis, ulcerative proctitis, ulcerative proctosigmoiditis, by rectum (retention enema), ADULT 100 mg at night for 21 days or until clinical and proctological remission; if no clinical and proctological improvement after 21 days, discontinue; treatment for 2–3 months may be required for proctological remission; when used for more than 21 days, discontinue gradually using 100 mg every other night for 2–3 weeks

Adverse effects:
local pain or burning sensation; rectal bleeding (reported with use of enema); exacerbation of untreated infections; suppositories may stain fabrics; systemic adverse effects (section 18.1)

SULFASALAZINE

Sulfasalazine is a representative aminosalicylate. Various drugs can serve as alternatives
Tablets, sulfasalazine 500 mg
Suppositories, sulfasalazine 500 mg
Retention enema (Rectal solution), sulfasalazine 3 g, 100-ml bottle

Uses:
ulcerative colitis; Crohn disease; severe rheumatoid arthritis (section 2.4)

Contraindications:
hypersensitivity to salicylates or sulfonamides; child under 2 years; porphyria; intestinal or urinary obstruction; severe renal impairment

Precautions:
renal impairment (Appendix 4); hepatic impairment; G6PD deficiency; slow acetylator status; monitor blood counts and liver
function initially and at monthly intervals for first 3 months; monitor kidney function initially and at intervals during treatment; history of allergy; pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

**Blood disorders.** Patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise occurring during treatment; blood count should be performed and sulfasalazine stopped immediately if there is suspicion or evidence of blood disorder

**Dosage:**

Ulcerative colitis, *by mouth*, **ADULT** 1–2 g 4 times daily in acute attack until remission, reducing to maintenance dose of 500 mg 4 times daily; **CHILD** over 2 years, 40–60 mg/kg daily in acute attack, reducing to maintenance dose of 20–30 mg/kg daily

Active Crohn disease, *by mouth*, **ADULT** 1–2 g 4 times daily in acute attack until remission occurs; **CHILD** over 2 years, 40–60 mg/kg daily in acute attack

Ulcerative colitis, Crohn colitis, *by rectum* (suppositories, used alone or in conjunction with oral therapy), **ADULT** 0.5–1 g morning and evening after a bowel movement; *by rectum* (retention enema), **ADULT** 3 g at night retained for at least an hour; **CHILD** not a suitable formulation

**Adverse effects:**

nausea, exacerbation of colitis; diarrhoea, loss of appetite, fever, blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, thrombocytopenia); hypersensitivity reactions (including rash, urticaria, Stevens-Johnson syndrome (erythema multiforme), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, lupus erythematosus-like syndrome); lung complications (including eosinophilia, fibrosing alveolitis); ocular complications (including periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, headache, hallucinations; kidney reactions (including proteinuria, crystalluria, haematuria); oligospermia; rarely acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained

Triamcinolone Acetonide

*Injection* (aqueous suspension), triamcinolone acetonide 40 mg/ml

**Uses:**

suppression of inflammation and allergic disorders

**Contraindications:**

systemic infections (unless specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished)

**Precautions:**

children and adolescents (growth retardation possibly irre-
versible), elderly (close supervision required particularly on long-term treatment

**Dosage:**
by deep intramuscular injection, into gluteal muscle, 40 mg of acetonide for depot effect, repeated at intervals according to the patient’s response; max. single dose 100 mg

**Side effects:**
minimized by using lowest effective dose for minimum period possible; gastro-intestinal effects include dyspepsia, peptic ulceration (with perforation), abdominal distension acute pancreatitis, oesophageal ulceration and acute candidiasis, musculoskeletal effects include proximal myopathy, osteoporosis, vertebral and long bone fractures (see under prednisolone)

### 17.5 Antispasmodic drugs

The smooth muscle relaxant properties of anticholinergic (more correctly termed antimuscarinic) and other antispasmodic drugs may be useful in dyspepsia, irritable bowel syndrome, and in diverticular disease. The gastric antisecretory effects of conventional anticholinergic drugs are of little practical significance since dosage is limited by atropine-like adverse effects. Moreover they have been superseded by more powerful and specific antisecretory drugs, including the histamine H₂-receptor antagonists.

Anticholinergics that are used for gastrointestinal smooth muscle spasm include atropine and hyoscine butylbromide.

#### ATROPINE SULFATE

Atropine sulfate is a representative antispasmodic drug. Various drugs can serve as alternatives

**Tablet** atropine sulfate 600 micrograms

**Uses:**
dyspepsia, irritable bowel syndrome, diverticular disease; premedication (section 1.3); mydriasis and cycloplegia (section 21.5); poisoning (section 4.2.3)

**Contraindications:**
angle-closure glaucoma; myasthenia gravis; paralytic ileus; pyloric stenosis; prostatic enlargement

**Precautions:**
children, elderly and Down syndrome (increased risk of adverse effects); gastro-oesophageal reflux; diarrhoea; ulcerative colitis; acute myocardial infarction; hypertension; hyperthyroidism; cardiac insufficiency; cardiac surgery—conditions characterized by tachycardia; pyrexia; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

**Dosage:**
Dyspepsia, irritable bowel syndrome, diverticular disease, by mouth, **ADULT** 0.6–1.2 mg at night

Adverse effects:
constipation; transient bradycardia (followed by tachycardia, palpitations and arrhythmias); reduced bronchial secretions, urinary urgency and retention; dilatation of pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of skin; occasionally confusion (particularly in the elderly), nausea, vomiting and giddiness

Hyoscine Butylbromide
Tablet, coated hyoscine butyl bromide, 10 mg
Injection, hyoscine butylbromide, 20 mg/ml

Uses:
symptomatic relief of gastro-intestinal or genito-urinary disorders characterized by smooth muscle spasm

Contraindications:
angle-closure glaucoma, myasthenia gravis (but may be used to decrease muscarinic side-effects of anticholinesterases), paralytic ileus, pyloric stenosis and prostatic enlargement; avoid in porphyria

Cautions:
use with caution in Down’s syndrome, in children and the elderly, in gastro-oesophageal reflux disease, diarrhoea, acute myocardial infarction, hypertension, conditions characterized by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, pregnancy and breast-feeding

Dosage:
by mouth (but poorly absorbed), 20 mg 4 times a daily; CHILD 6-12 years 10 mg 3 times daily
Irritable bowel syndrome, 10 mg 3 times daily, increased if required up to 20 mg 4 times daily
By intramuscular or slow intravenous injection, acute spasm and spasm in diagnostic procedures, 20 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 100 mg daily; CHILD not recommended

Adverse effects:
see under atropine

17.6 Laxatives

A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation.
Before prescribing laxatives, it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint. It is also important that the patient understands that bowel habit can vary considerably in frequency without doing harm. For example some people consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient’s own
normal pattern and this should be explained to the patient since misconceptions about bowel habits have led to excessive laxative use which in turn has led to hypokalaemia and an aonic non-functioning colon.

Laxatives should generally be avoided except where straining will exacerbate a condition such as angina or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are of value in drug-induced constipation, for the expulsion of parasites after anthelmintic treatment and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is rarely necessary except occasionally in the elderly.

There are many different laxatives. These include bulk-forming laxatives which relieve constipation by increasing faecal mass and stimulating peristalsis, stimulant laxatives which increase intestinal motility and often cause abdominal cramp, faecal softeners which lubricate and soften impacted faeces and osmotic laxatives which act by retaining fluid in the bowel by osmosis. Bowel cleansing solutions are used before colonic surgery, colonoscopy or radiological examination to ensure that the bowel is free of solid contents; they are not a treatment for constipation.

**BISACODYL**

Bisacodyl is a representative stimulant laxative. Various drugs can serve as alternatives

- **Tablets**, bisacodyl 5 mg total sennosides
- **Suppository**, bisacodyl 10mg, 5 mg (paediatric)

**Uses:**
constipation;

**Contraindications:**
intestinal obstruction; undiagnosed abdominal symptoms

**Precautions:**
Avoid prolonged use unless indication for prevention of faecal impaction; breastfeeding (Appendix 3)

**Dosage:**
- **Constipation, by mouth**, 5-10 mg at night; CHILD 4-10 years (on medical advice only) 5 mg at night, over 10 years, adult dose.
- By rectum in suppositories, 10 mg in the morning; CHILD under 10 years (on medical advice only) 5 mg, over 10 years, adult dose
- Before radiological procedures and surgery, by mouth, 10-20 mg the night before procedure and by rectum in suppositories, 10 mg the following morning; CHILD 4-10 years by mouth, 5 mg the night before the procedure and by rectum in suppositories, 5 mg the following morning, over 10 years, adult dose

**Adverse effects:**

abdominal discomfort; atonic non-functioning colon and hypokalaemia (with prolonged use or overdosage)

17.6.1 Drugs used in diarrhoea

Acute diarrhoeal diseases are a leading cause of childhood morbidity and mortality; frail and elderly patients are also at risk. In adults acute diarrhoea is the most frequent health problem of travellers to developing countries and is increasingly common among HIV-infected persons. Assessment and correction of dehydration and electrolyte disturbance is the priority in all cases of acute diarrhoea. Symptomatic relief (section 17.7.2) in adults may be warranted in some cases but antidiarrhoeals should never be used in children since they do not reduce fluid and electrolyte loss and may cause adverse effects.

Diarrhoea persisting for longer than a month is known as chronic diarrhoea. A mild malabsorption syndrome, tropical enteropathy, is apparent in most healthy indigenous populations of tropical countries. However the majority of cases of chronic diarrhoea have non-infectious causes including gluten-sensitivity, inherited metabolic disorders or inflammatory bowel disease.

Bloody diarrhoea is usually a sign of invasive enteric infection and should be treated with an appropriate anti-infective agent.

17.6.2 Oral rehydration

Acute diarrhoea in children should always be treated with oral rehydration solution according to plan A, B or C as shown. Severely dehydrated patients must be treated initially with intravenous fluids until they are able to take fluids by mouth. For oral rehydration it is important to administer the solution in small amounts at regular intervals as indicated below.

Treatment of dehydration: WHO recommendations

According to the degree of dehydration, health professionals are advised to follow one of 3 management plans.

**Plan A: no dehydration.** Nutritional advice and increased fluid intake are sufficient (soup, rice, water and yoghurt, or even water). For infants aged under 6 months who have not yet started taking solids, oral rehydration solution must be presented before offering milk. Mother’s milk or dried cow’s milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of breastfeeding must be increased.

**Plan B: moderate dehydration.** Whatever the child’s age, a 4-hour treatment plan is applied to avoid short-term problems. Feeding should not therefore be envisaged initially. It is recommended that parents are shown how to give approximately 75
ml/kg of oral rehydration solution with a spoon 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 can be given if the child continues to have frequent stools. In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate (about one teaspoonful every 2 minutes). The child’s status must be re-assessed after 4 hours to decide on the most appropriate subsequent treatment. 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. In hospital (or elsewhere), if the child can drink, oral rehydration solution must be given pending, and even during, intravenous infusion (20 ml/kg every hour by mouth before infusion, then 5 ml/kg every hour by mouth during intravenous rehydration). For intravenous supplementation, it is recommended that compound solution of sodium lactate (see section 26.2) is administered at a rate adapted to the child’s age (infant under 12 months: 30 ml/kg over 1 hour then 70 ml/kg over 5 hours; child over 12 months: the same amounts over 30 minutes and 2.5 hours respectively). If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution, at a rate of 20 ml/kg every hour. If the child vomits, the rate of administration of the oral solution should be reduced.

**Glucose salt solution**
- sodium chloride: 2.6 g/litre of clean water
- sodium citrate: 2.9 g/litre of clean water
- potassium chloride: 1.5 g/litre of clean water
- Glucose (anhydrous): 13.5 g/litre of clean water

When glucose and sodium citrate are not available, they may be replaced by

- sucrose (common sugar): 27 g/litre of clean water
- sodium bicarbonate: 2.5 g/litre 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

**CHOLERA.**

In cases of cholera, oral rehydration salts containing a higher concentration of sodium may be required to prevent hyponatraemia

**Uses:**
dehydration from acute diarrhoea

**Precautions:**
renal impairment

**Dosage:**
Fluid and electrolyte loss in acute diarrhoea, by mouth, ADULT 200–400 ml solution after every loose motion; INFANT and CHILD according to Plan A, B or C (see notes above)

**Adverse effects:**
vomiting—may indicate too rapid administration; hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution

### Antimotility drugs

Opioids such as codeine are used in the symptomatic relief of uncomplicated, acute diarrhoea in adults but not in young children. They act on opioid receptors in the gut wall and decrease bowel motility. In dehydration, fluid and electrolyte replacement (section 17.7.1) are of primary importance.

**Loperamide Hydrochloride**

**Tablet**, loperamide hydrochloride 2 mg

**Uses:**
symptomatic treatment of acute diarrhea; adjunct to rehydration in acute diarrhoea in adults and children over 4 years; chronic diarrhea in adults only

**Contraindications:**
conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as ulcerative colitis or antibiotic-associated colitis

**Precautions:**
liver disease, pregnancy and breast-feeding

**Dosage:**
acute diarrhea, 4 mg initially followed by 2 mg after each loose stool for up to 5 days, usually 6–8 mg daily; max. 16 mg daily; CHILD under 4 years not recommended, 4-8 years 1 mg 3-4 times daily for up to 3 days only, 9-12 years 2 mg 4 times daily for up to 5 days

Chronic diarrhea in adults, 4-8 mg daily in divided doses, subsequently adjusted according to response and given in two divided doses for maintenance; max. 16 mg daily

**Adverse effects:**
abdominal cramps, dizziness, drowsiness, and skin reactions, including urticariareported; paralytic ileus and abdominal bloating also reported
17.8 Antimotility drugs
SECTION 18: HORMONES AND OTHER ENDOCRINE DRUGS AND CONTRACEPTIVES

18.1 Adrenal hormones and synthetic substitutes
18.2
18.3 Contraceptives
18.3.1 Hormone contraceptives
18.3.2 Insulins and other antidiabetic agents
18.3.3 Barrier methods
18.4 Estrogen
18.5 Progestogens
18.6 Ovulation inducers
18.7 Insulin and other antidiabetic drugs
18.8 Thyroid hormones and antithyroid medicines
18.8.1 Thyroid hormones
18.8.2 Antithyroid drugs
Hormones and other endocrine drugs and contraceptives

18.1 Adrenal hormones and synthetic substances

Corticosteroids (section 3.1) include hormones secreted by the adrenal cortex and synthetic analogues of these hormones. The adrenal cortex normally secretes hydrocortisone which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone. Synthetic glucocorticoids include betamethasone, dexamethasone and prednisolone. Fludrocortisone has glucocorticoid properties but it has potent mineralocorticoid properties and is used for its mineralocorticoid effects.

Pharmacology of the corticosteroids is complex and their actions are wide-ranging. In physiological (low) doses, they replace deficient endogenous hormones. In pharmacological (high) doses, glucocorticoids decrease inflammation and suppress the immune response.

In therapeutic doses glucocorticoids suppress release of corticotrophin (adrenocorticotropic hormone, ACTH) from the pituitary thus the adrenal cortex ceases secretion of endogenous corticosteroids. If suppressive doses are given for prolonged periods, the adrenal cortex may atrophy and this leads to a deficiency on sudden withdrawal or dosage reduction or situations such as stress or trauma where corticosteroid requirements are increased. After high dosage or prolonged therapy, withdrawal should be gradual, the rate depending on various factors including patient response, corticosteroid dose, duration of treatment and disease state. The suppressive action of a corticosteroid on cortisol secretion is least when given in the morning. Corticosteroids should normally be given in a single morning dose to attempt to minimize pituitary-adrenal suppression. Because the therapeutic effects of corticosteroids are of longer duration than the metabolic effects, intermittent therapy may allow the body’s normal metabolic rhythm and the therapeutic effects to be maintained. Alternate day dosing is, however, suitable only in certain disease states and with corticosteroids with small mineralocorticoid effects and a relatively short duration of action.

Hydrocortisone is used in adrenal replacement therapy and on a short-term basis by intravenous injection for the emergency management of some conditions. Its mineralocorticoid activity is too high for it to be used on a long-term basis for disease suppression. The mineralocorticoid activity of fludrocortisone is also high and its anti-inflammatory activity is of no clinical relevance. It is used together with glucocorticoids in adrenal insufficiency. Prednisolone has predominantly glucocorticoid activity and is the corticosteroid most commonly administered.
for long-term disease suppression. It is the active metabolite of prednisone, conversion of which is variable and prednisone should not be used interchangeably with prednisolone. Dexamethasone has very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity making it particularly suitable for high-dose therapy in conditions where water retention would be a disadvantage such as cerebral oedema. It also has a long duration of action and this, together with its lack of mineralocorticoid activity makes it particularly suitable for conditions requiring suppression of corticotrophin secretion such as congenital adrenal hyperplasia.

Disadvantages of corticosteroids
Overdosage or prolonged use may exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid adverse effects. Mineralocorticoid adverse effects include hypertension, sodium and water retention and potassium loss. These effects are most marked with fludrocortisone but are significant with hydrocortisone, occur slightly with prednisolone and are negligible with dexamethasone.

Glucocorticoid adverse effects include diabetes mellitus and osteoporosis which is of particular importance in the elderly since it may result in osteoporotic fractures of the hip or vertebrae. High doses may also be associated with avascular necrosis of the femoral neck. Muscle wasting may also occur and there is a weak link with peptic ulceration. Mental disturbances can occur, including serious paranoid state or depression with risk of suicide, particularly in patients with a history of mental disorders; euphoria is also common. High doses may cause Cushing syndrome (typical moon face, striae and acne), which is usually reversible on withdrawal of treatment, but this should always be tapered gradually to avoid symptoms of acute adrenal insufficiency (see also Withdrawal). In children, corticosteroids may result in suppression of growth and corticosteroids administered during pregnancy can affect adrenal development in the fetus. Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important. Healing of wounds may be impaired and infections and thinning of the skin may occur; spread of infections may result from modification of tissue reactions.

Adrenal suppression
Adrenal suppression occurs during prolonged therapy with corticosteroids, with development of adrenal atrophy which may persist for years after stopping. Abrupt withdrawal after a prolonged period may lead to acute adrenal insufficiency, hypotension or death (see Withdrawal of Systemic Corticosteroids, below). Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin
nodules and weight loss.

CORTICOSTEROID COVER DURING STRESS
To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgery requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. Anaesthetists must therefore know whether a patient is taking or has been taking a corticosteroid, to avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- **Minor surgery under general anaesthesia** — usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25–50 mg intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery
- **Moderate or major surgery** — usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25–50 mg intravenously at induction, followed by hydrocortisone 25–50 mg 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual preoperative oral corticosteroid dose is recommenced on stopping hydrocortisone injections

Infections
Prolonged courses of corticosteroids increase susceptibility to infections and increase their severity; clinical presentation of infections may also be atypical. Serious infections, for example septicaemia and tuberculosis, may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.

CHICKENPOX
Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunization with varicella–zoster immunoglobulin [not included on WHO Model List] is needed for exposed non-immune patients receiving systemic corticosteroids or

for those who have used them within the previous 3 months; varicella–zoster immunoglobulin should preferably be given within 3 days of exposure and no later than 10 days. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased. Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

MEASLES
Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin [not included on WHO Model List] may be needed.

Dosage and administration
Adverse effects of systemic glucocorticoids, including suppression of the HPA (hypothalamo-pituitary-adrenal) axis, are dose- and duration-dependent; thus patients should be given treatment for the shortest period at the lowest dose that is clinically necessary. Patient response is variable and doses should therefore be individualized. In life-threatening diseases, high doses may be needed because the complications of therapy are likely to be less serious than the disease. In long-term therapy in relatively benign chronic conditions such as rheumatoid arthritis, adverse effects often outweigh the advantages. In order to minimize the adverse effects, the maintenance dose should be kept as low as possible and if possible, single morning doses or alternate day therapy should be used. Glucocorticoids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis and polyarteritis nodosa; in such disorders the effects of the disease process may be suppressed and symptoms relieved but the underlying condition is not cured. Glucocorticoids are used both topically and systemically. In emergency situations, hydrocortisone may be given intravenously; in the treatment of asthma, inhalation therapy with beclometasone may be used (section 25.1). Whenever possible, local treatment with creams, intra-articular injections, inhalations, eye-drops or enemas should be used in preference to systemic therapy.

Withdrawal of systemic corticosteroids
The rate of withdrawal of systemic glucocorticoids is dependent upon several factors including size of dose, duration of treatment, individual patient’s response and the likelihood of relapse of the underlying disease. If there is uncertainty about suppression of the HPA axis, 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. Gradual withdrawal should be considered in those whose disease is unlikely to relapse and who have:

- recently received repeated courses (particularly if taken for longer than 3 weeks)
- taken a short course within 1 year of stopping long-term therapy
- other possible causes of adrenal suppression
- received more than 40 mg daily prednisolone (or equivalent)
- been given repeat doses in the evening
- received more than 3 weeks' treatment

Abrupt withdrawal may be considered in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to the physiological dosage (equivalent to 7.5 mg prednisolone daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

**DEXAMETHASONE**

*Injection* (Solution for injection), dexamethasone phosphate (as dexamethasone sodium phosphate) 4 mg/ml, 1-ml ampoule

**Uses:**

- suppression of inflammatory and allergic disorders (see also allergy and allergic disorders, section 3.1);
- shock;
- diagnosis of Cushing syndrome;
- congenital adrenal hyperplasia;
- cerebral oedema

**Contraindications:**

See notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunsuppressive doses (serum antibody response diminished)

**Precautions:**

- adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above);
- ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks;
- monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout prolonged treatment;
- infections (greater susceptibility, symptoms may be masked until advanced stage; clinical presentation may be atypical; risk of chickenpox and measles increased (see notes above);
- quiescent tuberculosis—chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension,
recent myocardial infarction (rupture reported), congestive heart failure, liver failure, renal impairment, diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma including family history, severe affective disorder (particularly if history of steroid-induced psychosis), epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Suppression of inflammation and allergic disorders by intramuscular injection or slow intravenous injection or intravenous infusion (as dexamethasone phosphate), ADULT initially 0.5–20 mg daily; CHILD 200–500 micrograms/kg daily
Cerebral oedema, by intravenous injection (as dexamethasone phosphate), ADULT 10 mg initially, then 4 mg by intramuscular injection (as dexamethasone phosphate) every 6 hours, as required for 2–10 days
Diagnosis of Cushing syndrome, see manufacturer’s literature

NOTE.
Dexamethasone 1 mg = dexamethasone phosphate 1.2 mg = dexamethasone sodium phosphate 1.3 mg

Adverse effects:
gastrointestinal effects including dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophageal ulceration and candidiosis; musculoskeletal effects including proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture; endocrine effects including adrenal suppression, menstrual irregularities and amenorrhoea, Cushing syndrome (with high doses, usually reversible on withdrawal), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite, increased susceptibility to and severity of infection; neuropsychiatric effects including euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects including glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease; also impaired healing, skin atrophy, bruising, striae, telangiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbances, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise and hiccups; perineal irritation may follow intravenous administration of phosphate ester

HYDROCORTISONE

Injection (Powder for solution for injection), hydrocortisone (as sodium succinate) 100-mg vial

Uses:
adrenocortical insufficiency; hypersensitivity reactions including anaphylactic shock (section 3.1); inflammatory bowel disease (section 17.4); skin (section 13.3); asthma (section 25.1)

Contraindications:
see notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished)

Precautions:
adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above); ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks; monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout prolonged treatment; infections (greater susceptibility, symptoms may be masked until advanced stage; clinical presentation may be atypical; risks of chickenpox and measles increased (see notes above); quiescent tuberculosis—chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension, recent myocardial infarction (rupture reported), congestive heart failure, liver failure, renal impairment, diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma including family history, severe affective disorder (particularly if history of steroid-induced psychosis), epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Acute adrenocortical insufficiency, by slow intravenous injection or by intravenous infusion, ADULT 100–500 mg, 3–4 times in 24 hours or as required; by slow intravenous injection, CHILD up to 1 year 25 mg, 1–5 years 50 mg, 6–12 years 100 mg

Reconstitution and Administration.
According to manufacturer’s directions

Adverse effects:
gastrointestinal effects including dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophageal ulceration and candidosis; musculoskeletal effects including proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture; endocrine effects including adrenal suppression,
menstrual irregularities and amenorrhea, Cushing syndrome (with high doses, usually reversible on withdrawal), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite, increased susceptibility to and severity of infection; neuropsychiatric effects including euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects including glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease; also impaired healing, skin atrophy, bruising, striae, telangiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbances, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise and hiccups

**PREDNISOLONE**

Prednisolone is a representative corticosteroid. Various drugs can serve as alternatives

**Tablets**, prednisolone 5 mg, 25 mg

**Uses:**
suppression of inflammatory and allergic reactions (see also section 3.1); with antineoplastic drugs for acute leukaemias and lymphomas (section 8.3); eye (section 21.2); asthma (section 25.1)

**Contraindications:**
see notes above; systemic infection (unless life-threatening or specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished)

**Precautions:**
adrenal suppression during prolonged treatment which persists for years after stopping treatment (see notes above); ensure patients understand importance of compliance with dosage and have guidance on precautions to reduce risks; monitor weight, blood pressure, fluid and electrolyte balance and blood glucose levels throughout prolonged treatment; infections (greater susceptibility, symptoms may be masked until advanced stage; clinical presentation may be atypical; risk of chickenpox and measles increased (see notes above); quiescent tuberculosis—chemoprophylactic therapy during prolonged corticosteroid treatment; elderly; children and adolescents (growth retardation possibly irreversible); hypertension, recent myocardial infarction (rupture reported), congestive heart failure, renal impairment, hepatic impairment (Appendix 5); diabetes mellitus including family history, osteoporosis (may be manifested as back pain, postmenopausal women at special risk), glaucoma

including family history, severe affective disorder (particularly if history of steroid-induced psychosis), epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; pregnancy (Appendix 2); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Suppression of inflammatory and allergic disorders, by mouth, ADULT initially up to 10–20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; dose can often be reduced within a few days, but may need to be continued for several weeks or months; CHILD fractions of adult dose may be used (for example, at 1 year 25% of adult dose, at 7 years 50%, and at 12 years 75%) but clinical factors must be given due weight

Dosage:
ADULT initially up to 10–20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; dose can often be reduced within a few days, but may need to be continued for several weeks or months; CHILD fractions of adult dose may be used (for example, at 1 year 25% of adult dose, at 7 years 50%, and at 12 years 75%) but clinical factors must be given due weight

Maintenance, by mouth, ADULT 2.5–15 mg daily or higher; cushingoid features are increasingly likely with doses above 7.5 mg daily; CHILD fractions of adult dose may be used (for example, at 1 year 25% of adult dose, at 7 years 50%, and at 12 years 75%) but clinical factors must be given due weight

Myasthenia gravis, initially 10 mg on alternate days, increased in steps of 10 mg on alternate days to 1–1.5 mg/kg (maximum 100 mg) on alternate days or initially 5 mg daily increased in steps of 5 mg daily to usual dose of 60–80 mg daily (0.75–1 mg/kg daily)

Adverse effects:
gastrointestinal effects including dyspepsia, peptic ulceration (with perforation), abdominal distension, acute pancreatitis, oesophageal ulceration and candidosis; musculoskeletal effects including proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture; endocrine effects including adrenal suppression, menstrual irregularities and amenorrhoea, Cushing syndrome (with high doses, usually reversible on withdrawal), hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite, increased susceptibility to and severity of infection; neuropsychiatric effects including euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), psychosis and aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects including glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease; also impaired healing, skin atrophy, bruising, striae, telangiectasia, acne, myocardial rupture following recent myocardial infarction, fluid and electrolyte disturbances, leukocytosis, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise and hiccups

Androgens

Androgens are secreted by the testes and weaker androgens by the adrenal cortex and ovaries. In the male, they are responsible for the development and maintenance of the sex organs and the secondary sexual characteristics, normal reproductive function, and sexual performance ability in addition to stimulating the growth and development of the skeleton and skeletal muscle during puberty. At high doses in the normal male androgens inhibit pituitary gonadotrophin secretion and depress spermatogenesis. **Testosterone** is used as replacement therapy in those who are hypogonadal due to either pituitary (secondary hypogonadism) or testicular disease (primary hypogonadism). Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated and treatment should always be under expert supervision. When given to patients with hypopituitarism they can lead to normal sexual development and potency but not fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production. Androgens cannot induce fertility in men with primary hypogonadism. Caution should be used in treating boys with delayed puberty with excessive doses of testosterone since the fusion of epiphyses is hastened and may result in short stature. Androgens, including testosterone have also been used in postmenopausal women for the palliative treatment of androgen-responsive, advanced, metastatic breast cancer; care is required to prevent masculinizing effects.

18.3 Contraceptives

18.3.1 Hormonal contraceptives

Hormonal contraception is one of the most effective methods of reversible fertility control.

**COMBINED ORAL CONTRACEPTIVES**

Estrogen plus progestogen combinations are the most widely used hormonal contraceptives. They produce a contraceptive effect mainly by suppressing the hypothalamic-pituitary system resulting in prevention of ovulation; in addition, changes in the endometrium make it unreceptive to implantation. Endometrial proliferation is usually followed by thinning or regression of the endometrium resulting in reduced menstrual flow. Ovulation usually resumes within three menstrual cycles after oral contraception has been discontinued; anovulation and amenorrhoea persisting for six months or longer requires investigation and appropriate treatment if necessary.

Potential non-contraceptive benefits of combined oral contraceptives include improved regularity of the menstrual cycle, decreased blood loss, less iron-deficiency anaemia and significant decrease in dysmenorrhea. Long-term use is associated with reduced risk of endometrial and ovarian cancer and of some pelvic infections.

An association between the amount of estrogen and progestogen in oral contraceptives and an increased risk of adverse cardiovascular effects has been observed. The use of oral contraceptive combinations containing the progestogens, desogestrel or gestodene are associated with a slightly increased risk of venous thromboembolism compared with oral contraceptives containing the progestogens, levonorgestrel or norethisterone.

**RISK FACTORS FOR VENOUS THROMBOEMBOLISM OR ARTERIAL DISEASE**

Risk factors for *venous thromboembolism* include family history of venous thromboembolism in first-degree relative aged under 45 years, obesity, long-term immobilization and varicose veins.

Risk factors for *arterial disease* include family history of arterial disease in first-degree relative aged under 45 years, diabetes mellitus, hypertension, smoking, age over 35 years (avoid if over 50 years), obesity and migraine.

If any one of the factors is present, combined oral contraceptives should be used with caution; if 2 or more factors for either venous thromboembolism or arterial disease are present, combined oral contraceptives should be avoided. Combined oral contraceptives are contraindicated in migraine with aura, in severe migraine without aura regularly lasting over 72 hours despite treatment and in migraine treated with ergot derivatives.

**SURGERY**

Estrogen-containing oral contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilization of a lower limb. They should normally be restarted at the first menses occurring at least 2 weeks after full mobilization. When discontinuation is not possible thromboprophylaxis (with heparin and graduated compression hosiery) is advised.

**REASONS TO STOP COMBINED ORAL CONTRACEPTIVES IMMEDIATELY**

Combined estrogen-containing oral contraceptives should be stopped immediately if any of the following symptoms occur and
resumed only after consultation with a health care provider:

- Sudden severe chest pain (even if not radiating to left arm);
- Sudden breathlessness (or cough with blood-stained sputum);
- Severe pain in calf of one leg;
- Severe stomach pain;
- Serious neurological effects including unusual, severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphagia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- Hepatitis, jaundice, liver enlargement;
- Blood pressure above systolic 160 mmHg and diastolic 100 mmHg;
- Detection of 2 or more risk factors for venous thromboembolism or arterial disease, see notes above

PROGESTOGEN-ONLY CONTRACEPTIVES

Progestogen-only contraceptives, such as oral levonorgestrel may offer a suitable alternative when estrogens are contraindicated but the oral progestogen-only preparations do not prevent ovulation in all cycles and have a higher failure rate than combined estrogen-containing preparations. Progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives and are preferable for women at increased risk of such complications, for example smokers over 35 years. They can be used as an alternative to estrogen-containing combined preparations prior to major surgery. Oral progestogen-only contraceptives may be started 3 weeks after birth; breastfeeding women should preferably start at least 6 weeks after birth. Menstrual irregularities (oligomenorrhoea, menorrhagia, amenorrhoea) are common. Injectable preparations of medroxyprogesterone acetate or norethisterone enantate may be given intramuscularly. They have prolonged action and should only be given with full counselling and manufacturer’s information leaflet.

EMERGENCY CONTRACEPTION

Levonorgestrel is used for emergency contraception. Levonorgestrel 1.5 mg should be taken as a single dose within 120 hours of unprotected intercourse; alternatively, levonorgestrel 750 micrograms can be taken within 72 hours of unprotected intercourse followed 12 hours later by another 750 micrograms. Under these circumstances levonorgestrel
prevents about 86% of pregnancies that would have occurred if no treatment had been given. Adverse effects include nausea, vomiting, headache, dizziness, breast discomfort, and menstrual irregularities. If vomiting occurs within 2–3 hours of taking the tablets, replacement tablets can be given with an antiemetic.

It should be explained to the woman that her next period may be early or late; that she needs to use a barrier contraceptive method until her next period, and that she should return promptly if she has any lower abdominal pain or if the subsequent menstrual bleed is abnormally light, heavy, brief or absent. There is no evidence of harmful effects to the fetus if pregnancy should occur.

**MEDROXYPROGESTERONE ACETATE**

depoprovera

Medroxyprogesterone acetate is a complementary drug Injection (Suspension for injection), medroxyprogesterone acetate 150 mg/ml, 1-ml vial

**Uses:**

parenteral progestogen-only contraception (short-term or long-term); menstrual symptoms and endometriosis (section 18.5)

**Contraindications:**

pregnancy (Appendix 2); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); severe arterial disease; porphyria

**Precautions:**

small increase in possible risk of breast cancer; migraine; liver disease; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease; interactions: Appendix 1

**Dosage:**

Contraception (short-term), by deep intramuscular injection, ADULT (female) 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breastfeeding)

Contraception (long-term), by deep intramuscular injection, ADULT (female) as for short-term, repeated every 3 months

**ADMINISTRATION.**

If interval between injections is greater than 3 months and 14 days, exclude pregnancy before next injection and advise patient to use additional contraceptive measures (for example barrier) for 7 days after the injection

**Patient Advice.**

Women must receive full counselling (backed by manufacturer’s approved leaflet) before treatment, concerning menstrual irregularities and because of prolonged activity and the potential

for a delay in return to full fertility

**Adverse effects:**
menstrual irregularities; delayed return to fertility; reduction in bone mineral density; weight gain; depression; rarely, anaphylaxis

**Norethisterone enantate**  
**(primolut)**

*Oily injection* (Solution for injection), norethisterone enantate 200 mg/ml, 1-ml ampoule

**Uses:**
parenteral progestogen-only contraception (short-term)

**Contraindications:**
pregnancy (Appendix 2); breast or endometrial cancer; severe liver disease (Dubin-Johnson or Rotor syndromes) (Appendix 5); history during pregnancy of jaundice, pruritus, herpes or of deteriorating otosclerosis; severe diabetes mellitus with vascular changes; hypertension; 12 weeks before planned surgery and during immobilization; thromboembolic disease; disturbances of lipid metabolism; undiagnosed vaginal bleeding; porphyria

**Precautions:**
possible small increase in risk of breast cancer; migraine; liver dysfunction; depression; diabetes mellitus; previous ectopic pregnancy; cardiac and renal disease; **interactions:** Appendix 1

**Dosage:**
Short-term contraception, by **deep intramuscular injection** into gluteal muscle, **ADULT** (female) 200 mg within 5 days of cycle or immediately after parturition; repeated after 2 months

**Administration.**
If interval between injections is greater than 2 months and 14 days, exclude pregnancy before next injection and advise patient to use additional contraceptive measures (for example barrier) for 7 days after the injection

**Patient Advice.**
Women must receive full counselling (backed by manufacturer’s approved leaflet) before treatment, concerning possible menstrual irregularities and because of prolonged activity **Adverse effects:** bloating, breast discomfort, headache, dizziness, depression, nausea, menstrual irregularities; rarely, weight gain

**Intrauterine contraceptive devices**
Copper-bearing intrauterine contraceptive devices consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of copper. Smaller devices have been introduced to minimize adverse effects and the replacement time for these devices is normally between 3 and 8 years. Fertility declines with age and
therefore a copper intrauterine device fitted in a woman over 40 years of age, may remain in the uterus until menopause. The intrauterine device is appropriate for women who expect to use it for continuous long-term contraception. It is suitable for older parous women; intrauterine devices should be used with caution in young nulliparous women because of the increased risk of expulsion. Young women at risk of sexually transmitted infections are also at risk of pelvic inflammatory disease. The timing and technique of fitting an intrauterine device play a critical part in its subsequent performance and call for proper training and experience. Patients should receive full counselling backed by the manufacturer’s approved leaflet. For routine contraception the device can be inserted between 4 and 12 days after the start of menstruation; for emergency contraception the device can be inserted at any time in the menstrual cycle within 5 days of unprotected intercourse. There is an increased risk of infection for 20 days after insertion and this may be related to existing lower genital tract infection. Pre-screening (at least for chlamydia and gonorrhoea) should if possible be performed. If sustained pelvic or lower abdominal pain occur during the following 20 days after insertion of the device, the woman should be treated as having acute pelvic inflammatory disease. An intrauterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential (for example to treat severe pelvic infection) post-coital contraception should be considered. If the woman becomes pregnant, the device should be removed in the first trimester and the possibility of ectopic pregnancy considered; if the threads of the intrauterine device are already missing on presentation, the pregnancy is at risk of second trimester abortion, haemorrhage, pre-term delivery and infection. 

**EMERGENCY CONTRACEPTION**

Insertion of a copper intrauterine contraceptive device is a highly effective method of emergency contraception and is more effective than hormonal methods of emergency contraception. Sexually transmitted diseases should be tested for and insertion of the device should usually be covered by antibacterial prophylaxis.

**Barrier methods**

**NOTE.**

Barrier methods are not as effective in preventing conception as hormonal contraception and copper intrauterine devices. Spermicidal methods when used alone are generally considered relatively ineffective and such use is not recommended

**Barriers**, male latex condoms, male non-latex condoms or female non-latex condoms; diaphragm or cervical caps

**Uses:** contraception; for condoms, also to decrease risk of transmission of HIV and other sexually transmitted diseases
**Precautions:** oil-based products including baby oil, massage oil, lipstick, petroleum jelly, sun-tan oil can damage latex condoms and render them less effective as barrier method of contraception and as a protection from sexually transmitted infections (including HIV); if a lubricant required, use one that is water-based; male condom must be put on before the penis touches the vaginal area and the penis must not touch the vaginal area after the condom has been taken off; spermicides or diaphragm not suitable for women at high risk of HIV infection or with HIV infection

**Adverse effects:**

vaginal and cervical irritation (spermicides), toxic shock syndrome (diaphragm, cap)

**Estrogens**

Estrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia. They affect bone by increasing calcium deposition. They are secreted at varying rates during the menstrual cycle throughout the period of activity of the ovaries. During pregnancy, the placenta becomes the main source of estrogens. At the menopause, ovarian secretion declines at varying rates.

Estrogen therapy is given cyclically or continuously principally for contraception and for the alleviation of menopausal symptoms. If long-term therapy is required for menopausal hormone therapy a progestogen should be added to prevent cystic hyperplasia of the endometrium (or of endometrial foci in women who have had a hysterectomy) and possible transformation to cancer.

The palliative care of advanced inoperable, metastatic carcinoma of the breast in both men and postmenopausal women is another indication for estrogen therapy.

**Diethylstilboestrol**

Diethylstilboestrol is a synthetic nonsteroidal estrogen that has been used in the palliation of breast and prostate cancer

**Tablet, 5 mg**

**Uses:**
palliative treatment of breast and prostate cancer

**Contraindications:**
pregnancy

**Precautions:**
should be used with caution in those with cardiovascular disease or hepatic impairment;

**Dosage:**
Daily doses of 10-20 mg are occasionally used by mouth in the palliative treatment of malignant neoplasms of the breast in post-menopausal women. The usual dose in carcinoma of the prostate is 1-3 mg daily by mouth.

Adverse effects:
Dose–related adverse effects of diethylstilboestrol include nausea, fluid retention, and atrial and venous thrombosis, and these effects are common at doses used for palliation of cancer. Impotence and gynaecomastia occur in men, and withdrawal bleeding may occur in women, as may hypercalcaemia and bone pain in women treated for breast cancer.

HORMONE REPLACEMENT THERAPY (HRT)
Estrogens are used for replacement therapy in perimenopausal and menopausal women for the treatment of vasomotor instability, vulvar and vaginal atrophy associated with the menopause and for the prevention of osteoporosis. HRT should not be prescribed with the aim of reducing the incidence of heart disease. Hormone replacement therapy may be used for menopausal women whose lives are unduly inconvenienced by vaginal atrophy or vasomotor instability. Vaginal atrophy may respond to a short course of a vaginal estrogen preparation. Systemic treatment is needed for vasomotor and other symptoms of estrogen deficiency and can be given for up to 2–3 years; in women with a uterus (or endometrial foci), a progestogen should be added to reduce the risk of endometrial cancer. Medroxyprogesterone acetate (see also section 18.5) may be given in a dose of 10 mg daily for the last 12–14 days of each estrogen HRT cycle. Alternatively, norethisterone 1 mg daily may be given on the last 12–14 days of each 28-day estrogen cycle.

HRT should be considered for women with early natural or surgical menopause (before age 45 years) because they have a high risk of osteoporosis. Small doses of estrogen given systemically in the perimenopausal and postmenopausal period also diminish osteoporosis, but the slight increased risk of breast cancer needs to be taken into account. For early menopause, HRT can be given until the approximate age of natural menopause (until age 50 years).

For longer-term use of HRT in postmenopausal women (with a uterus or without a uterus), women must be made aware of the increased incidence of breast cancer and other adverse effects. Each decision to start HRT should be made on an individual basis, and treatment should be regularly reappraised (at least once a year). Factors such as corticosteroid therapy, family history of osteoporosis, thinness, lack of exercise, alcoholism or smoking, early menopause, fractures to the hip or forearm before age 65 years should be taken into account when considering the use of HRT; women of African origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

There is an increased risk of deep-vein thrombosis and of pulmonary embolism in women taking HRT. In women who
have predisposing factors such as a personal or family history of deep venous thrombosis or pulmonary embolism, severe varicose veins, obesity, surgery, trauma or prolonged bed-rest, the overall risk may outweigh the benefit.

Using HRT increases the risk of breast cancer slightly. The increased risk is related to the duration of HRT use and this excess risk disappears within about 5 years of stopping. The risk of breast cancer is greater with combined HRT (an estrogen and a progestogen) than with estrogen-only HRT (but estrogen alone may not be suitable for women with intact uterus, see above).

Epidemiological studies indicate that in women aged between 50 and 65 years not using HRT, about 32 cases of breast cancer will be diagnosed in every 1000 women. In those using HRT, the risk of breast cancer is increased as follows:

- Women using combined HRT with an estrogen and a progestogen for 5 years, about 6 additional cases in 1000; in those using combined HRT for 10 years, about 19 additional cases in 1000
- Women using estrogen-only HRT for 5 years, about 2 additional cases in 1000; in those using estrogen-only HRT for 10 years, about 5 additional cases in 1000.

HRT does not provide contraception. If a potentially fertile woman needs to use HRT, non-hormonal contraceptive measures are necessary.

Precautions for patients on HRT undergoing surgery and reasons to stop HRT are the same as those for hormonal contraceptives (see notes in section 18.3.1).

**ETHINYLESTRADIOL**

Ethinylestradiol is a representative estrogen. Various drugs can serve as alternatives

*Tablets*, ethinylestradiol 10 micrograms, 50 micrograms

**Uses:**

- hormone replacement for menopausal symptoms; osteoporosis prophylaxis; palliation in breast cancer in men and postmenopausal women; contraception in combination with a progestogen (section 18.3.1)

**Contraindications:**

- pregnancy; estrogen-dependent cancer; active thrombophlebitis or thromboembolic disorders or history of recent venous thromboembolism (unless already on anticoagulant therapy); undiagnosed vaginal bleeding; breastfeeding (Appendix 3); liver disease (where liver function tests have failed to return to normal), Dubin-Johnson and Rotor syndromes (or monitor
closely)

**Precautions:**
Progestogen may need to be added to regimen to reduce risk of endometrial cancer due to unopposed estrogen (see notes above); migraine (or migraine-like headache); history of breast nodules of fibrocystic disease—closely monitor breast status (risk of breast cancer, see notes above); uterine fibroids may increase in size; symptoms of endometriosis may be exacerbated; predisposition to thromboembolism (see notes above); presence of antiphospholipid antibodies; increased risk of gallbladder disease; hypophyseal tumours; porphyria.

**interactions:** Appendix 1

**Dosage:**
Hormone replacement, *by mouth*, ADULT (female) 10–20 micrograms daily
Palliation in breast cancer in postmenopausal women, *by mouth*, ADULT 0.1–1 mg 3 times daily

**Adverse effects:**
nausea and vomiting, abdominal cramps and bloating, weight increase; breast enlargement and tenderness; premenstrual-like syndrome; sodium and fluid retention; thromboembolism (see notes above); altered blood lipids; cholestatic jaundice; rashes and chloasma; changes in libido; depression, headache, migraine, dizziness, leg cramps (rule out venous thrombosis); contact lenses may irritate

Levonorgestrel/ethinylestradiol

**Progestogens**

**Progesterone** is a hormone secreted by the corpus luteum whose actions include induction of secretory changes in the endometrium, relaxation of uterine smooth muscle and production of changes in the vaginal epithelium. Progesterone is relatively inactive following oral administration and produces local reactions at site of injection. This has led to the development of synthetic progestogens including levonorgestrel, norethisterone and medroxyprogesterone. Where endometriosis requires drug treatment, it may respond to synthetic progestogens on a continuous basis. They may also be used for the treatment of severe dysmenorrhoea. In postmenopausal women receiving long-term estrogen therapy for hormone replacement, a progestogen needs to be added for women with an intact uterus to prevent hyperplasia of the endometrium (section 18.4).

Progestogens are also used in combined oral contraceptives and progestogen-only contraceptives (section 18.3.1).

**MEDROXYPROGESTERONE ACETATE**

Medroxyprogesterone acetate is a complementary progesto-
genic drug

**Tablets**, medroxyprogesterone acetate 5 mg

**Uses:**
endometriosis; dysfunctional uterine bleeding; secondary amenorrhoea; contraception (section 18.3.1); adjunct in HRT (section 18.4)

**Contraindications:**
pregnancy (Appendix 2); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); severe arterial disease; porphyria

**Precautions:**
small increase in possible risk of breast cancer; migraine; depression; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease; breastfeeding (Appendix 3); **interactions:** Appendix 1

**Dosage:**
Mild to moderate endometriosis, *by mouth*, **adult** 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle
Dysfunctional uterine bleeding, *by mouth*, **adult** 2.5–10 mg daily for 5 to 10 days beginning on day 16 to 21 of cycle for 2 cycles
Secondary amenorrhoea, *by mouth*, **adult** 2.5–10 mg daily for 5–10 days beginning on day 16 to 21 of cycle for 3 cycles

**Adverse effects:**
acne, urticaria, fluid retention, weight gain, gastrointestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles; depression, insomnia, somnolence, headache, alopecia, hirsutism; anaphylactoid reactions; rarely jaundice

**NORETHISTERONE**

**primulot**

**Tablets**, norethisterone 5 mg

**Uses:**
endometriosis; menorrhagia; severe dysmenorrhoea; contraception (section 18.3.1); HRT (section 18.4)

**Contraindications:**
pregnancy (Appendix 2); undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); severe arterial disease; breast or genital tract cancer; porphyria; history in pregnancy of idiopathic jaundice, severe pruritus or pemphigoid gestationis

**Precautions:**
epilepsy; migraine; diabetes mellitus; hypertension; cardiac or renal disease and those susceptible to thromboembolism; depression; breastfeeding (Appendix 3); **interactions**: Appendix 1

**Dosage:**

Endometriosis, by mouth, ADULT (female) 10 mg daily starting on fifth day of cycle (increased if spotting occurs to 20–25 mg daily, reduced once bleeding has stopped).

Menorrhagia, by mouth, ADULT (female) 5 mg three times daily for 10 days to stop bleeding; to prevent bleeding 5 mg twice daily from day 19 to 26 of cycle.

Dysmenorrhoea, by mouth, ADULT (female) 5 mg 2–3 times daily from day 5 to 24 for 3 to 4 cycles.

**Adverse effects:**
- acne, urticaria, fluid retention, weight increase, gastrointestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles, depression, insomnia, somnolence, headache, dizziness, alopecia, hirsutism, anaphylactoid-like reactions; exacerbation of epilepsy and migraine; rarely jaundice.

### 18.3.2 Insulins and other antidiabetic drugs

**Diabetes mellitus** is characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism. There are 2 principal types of diabetes.

- **Type 1 diabetes or insulin-dependent diabetes mellitus** is due to a deficiency of insulin caused by autoimmune destruction of pancreatic beta cells. Patients require administration of insulin.
- **Type 2 diabetes or non-insulin dependent diabetes mellitus** is due to reduced secretion of insulin or to peripheral resistance to the action of insulin. Patients may be controlled by diet alone, but often require administration of oral antidiabetic drugs or insulin. The energy and carbohydrate intake must be adequate but obesity should be avoided. In type 2 diabetes, obesity is one of the factors associated with insulin resistance. Diets high in complex carbohydrate and fibre and low in fat are beneficial. Emphasis should be placed on exercise and increased activity.

The aim of treatment is to achieve the best possible control of plasma glucose concentration and prevent or minimize complications including microvascular complications (retinopathy, albuminuria, neuropathy). Diabetes mellitus is a strong risk factor for cardiovascular disease; other risk factors such as smoking, hypertension, obesity and hyperlipidaemia should also be addressed.

**Insulin**

Appropriate insulin regimens should be worked out for each patient. Insulin requirements may be affected by variations in lifestyle (diet and exercise)—drugs such as corticosteroids, infections, stress, accidental or surgical trauma, puberty and...
18.3.2 Insulins and other antidiabetic drugs

pregnancy (second and third trimesters) may increase insulin requirements; renal or hepatic impairment and some endocrine disorders (for example Addison disease, hypopituitarism) or coeliac disease may reduce requirements. In pregnancy insulin requirements should be monitored frequently.

If possible patients should monitor their own blood-glucose concentration using blood glucose strips. Since blood-glucose concentration varies throughout the day, patients should aim to maintain blood-glucose concentration between 4 and 10 mmol/litre for most of the day while accepting that on occasions it will be higher; strenuous efforts should be made to prevent blood-glucose concentrations falling below 4 mmol/litre because of the risk of hypoglycaemia. Patients should be advised to look for troughs and peaks of blood glucose and to adjust their insulin dosage only once or twice a week. Insulin doses are determined on an individual basis, by gradually increasing the dose to optimise blood-glucose concentration while avoiding hypoglycaemia.

In the absence of blood-glucose monitoring strips, urine-glucose monitoring strips can be used; in fact this is the method of personal choice for many patients with Type 2 diabetes mellitus. It is less reliable than blood glucose but is easier and costs much less. All patients should monitor either blood- or urine-glucose concentration daily.

Hypoglycaemia is a potential complication in all patients treated with insulin or oral hypoglycaemic agents. The consequences of hypoglycaemia, include confusion, seizures, coma and cerebral infarction. Loss of warning of hypoglycaemia is common among insulin-treated patients and can be a serious hazard especially for drivers and those in dangerous occupations. Very tight control lowers the blood glucose concentration needed to trigger hypoglycaemic symptoms; increase in the frequency of hypoglycaemic episodes reduces the warning symptoms experienced by patients. Beta-blockers can also blunt hypoglycaemic awareness (and delay recovery). Some patients report loss of hypoglycaemic warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemic awareness. If a patient believes that human insulin is responsible for loss of warning it is reasonable to revert to animal insulin. To restore warning signs, episodes of hypoglycaemia must be reduced to a minimum; this involves appropriate adjustment of insulin dose and frequency, and suitable timing and quantity of meals and snacks.

Drivers need to be particularly careful to avoid hypoglycaemia. They should check their blood-glucose concentration before driving and, on long journeys, at intervals of approximately two hours; they should ensure that a supply of sugar is always

readily available. If hypoglycaemia occurs, the driver should stop the vehicle in a safe place, ingest a suitable sugar supply and wait until recovery is complete (may be 15 minutes or longer). Driving is particularly hazardous when hypoglycaemic awareness is impaired.

For sporadic physical activity, extra carbohydrate may need to be taken to avert hypoglycaemia. Blood glucose should be monitored before, during and after exercise. Hypoglycaemia can develop in patients taking oral antidiabetics, notably the sulfonylureas, but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for several hours and must be treated in hospital.

Diabetic ketoacidosis is a potentially lethal condition caused by an absolute or relative lack of insulin; it commonly occurs when adjustments to insulin dosage fail to compensate for increases in insulin requirements, for example during severe infection or major intercurrent illness. Diabetes ketoacidosis occurs mostly in patients with Type 1 diabetes mellitus. It also occurs in Type 2 diabetics who have a temporary need for insulin. Diabetic ketoacidosis is characterized by hyperglycaemia, hyperketonaemia and acidaemia with dehydration and electrolyte disturbances. It is essential that soluble insulin (and intravenous fluids) is readily available for its treatment.

Infections are more likely to develop in patients with poorly controlled diabetes mellitus. These should be treated promptly and effectively to avoid diabetic ketoacidosis.

Surgery. Particular attention should be paid to insulin requirements when a patient with diabetes undergoes surgery that is likely to need an intravenous infusion of insulin for longer than 12 hours. Soluble insulin should be given in intravenous infusion of glucose and potassium chloride (provided the patient is not hyperkalaemic), and adjusted to provide a blood-glucose concentration of between 7 and 12 mmol/litre. The duration of action of intravenous insulin is only a few minutes therefore the infusion must not be stopped unless the patient becomes frankly hypoglycaemic. For non-insulin dependent diabetics, insulin treatment is almost always required during surgery (oral hypoglycaemic drugs having been omitted).

Insulin must be given by injection because it is inactivated by gastrointestinal enzymes. Generally, insulin is given by subcutaneous injection into the upper arms, thighs, buttocks, or abdomen. There may be increased absorption from a limb, if the limb is used in strenuous exercise following the injection. It is essential to use only syringes calibrated for the particular concentration of insulin administered.

There are three main types of insulin preparations, classified according to duration of action after subcutaneous injection:
18.3.2 Insulins and other antidiabetic drugs

- those of short duration which have a relatively rapid onset of action, for example soluble or neutral insulin;
- those with an intermediate action, for example isophane insulin and insulin zinc suspension;
- those with a relatively slow onset and long duration of action, for example crystalline insulin zinc suspension.

**Soluble insulin**, when injected subcutaneously, has a rapid onset of action (after 30–60 minutes), a peak action between 2 and 4 hours, and a duration of action up to 8 hours. Soluble insulin by the intravenous route is reserved for urgent treatment and fine control in serious illness and perioperatively. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes.

When injected subcutaneously, **intermediate-acting insulins** have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours and a duration of action of 16–24 hours. They can be given twice daily together with short-acting insulin or once daily, particularly in elderly patients. They can be mixed with soluble insulin in the syringe, essentially retaining properties of each component.

The duration of action of different insulin preparations varies considerably from one patient to another and this needs to be assessed for every individual. The type of insulin used and its dose and frequency of administration depend on the needs of each patient. For patients with acute onset diabetes mellitus, treatment should be started with soluble insulin given 3 times daily with medium-acting insulin at bedtime. For those less seriously ill, treatment is usually started with a mixture of pre-mixed short- and medium-acting insulins (for example 30% soluble insulin with 70% isophane insulin) given twice daily. The proportions of soluble insulin can be increased in patients with excessive post-prandial hyperglycaemia.

Regimens should be developed by each country.

**SOLUBLE INSULIN**

*Injection* (Solution for injection), soluble insulin 10-ml vial; 100 units/ml, 10-ml vial

**Uses:**
diabetes mellitus; diabetic emergencies and at surgery; diabetic ketoacidosis or coma

**Precautions:**
see notes above; reduce dose in renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); **interactions**: Appendix 1

**Dosage:**
Diabetes mellitus, by subcutaneous injection, by intramuscular

Insulins and other antidiabetic drugs

**ADULT** and **CHILD** according to individual requirements

**Adverse effects:**
- Hypoglycaemia in overdose; localized, and rarely generalized allergic reactions; lipoatrophy at injection site

**INSULIN 70/30 SUSPENSION**

*Injection* (Suspension for injection), insulin zinc (mixed) 100 units/ml, 10-ml vial

**Uses:**
- Diabetes mellitus

**Contraindications:**
- Intravenous administration

**Precautions:**
- See notes above; reduce dose in renal impairment (Appendix 4); pregnancy and breastfeeding (Appendix 2 and Appendix 3); **interactions:** Appendix 1

**Dosage:**
- Diabetes mellitus, *by subcutaneous injection*, **ADULT** and **CHILD** according to individual requirements

**IMPORTANT.**
- Intravenous injection contraindicated

**Adverse effects:**
- Hypoglycaemia in overdose; localized, and rarely generalized allergic reactions; lipoatrophy at injection site

**ISOPHANE INSULIN**

*Injection* (Suspension for injection), isophane insulin 10-ml vial; 100 units/ml, 10-ml vial

**Uses:**
- Diabetes mellitus

**Contraindications:**
- Intravenous administration

**Precautions:**
- See notes above; reduce dose in renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

**Dosage:**
- Diabetes mellitus, *by subcutaneous injection*, **ADULT** and **CHILD** according to individual requirements

**IMPORTANT.**
- Intravenous injection contraindicated

**Adverse effects:**
- Hypoglycaemia in overdose; localized, and rarely generalized allergic reactions; lipoatrophy at injection site

**Oral antidiabetic drugs**
- Oral antidiabetic (hypoglycaemic) drugs are used for non-

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insulin-dependent diabetes mellitus in patients who do not respond to dietary adjustment and an increase in physical exercise. They are used to supplement the effect of diet and exercise. There are various types of oral antidiabetic agents. The most commonly used are the *sulfonylureas* and the *biguanide*, metformin.

Sulfonylureas act mainly by augmenting insulin secretion and are therefore only effective if there is some residual pancreatic beta-cell activity. They may occasionally lead to hypoglycaemia 4 hours or more after food. This may be dose-related and usually indicates excessive dose and it occurs more frequently with long-acting sulfonylureas such as *glibenclamide* and occurs particularly in the elderly. The sulfonylureas have the disadvantage that they may encourage weight gain. They should not be used during breastfeeding and caution is required in the elderly and those with renal or hepatic insufficiency because of the risk of hypoglycaemia. Insulin therapy is generally required during intercurrent illness such as myocardial infarction, coma, infection, and trauma, during surgery and also during pregnancy.

**Metformin** exerts its effect by decreasing gluconeogenesis and by increasing peripheral utilization of glucose. Metformin can only act in the presence of endogenous insulin therefore is effective only in diabetics with some residual functioning pancreatic islet cells. It is used as a first-line treatment in overweight non-insulin-dependent diabetic patients and in others when strict dieting and sulfonylureas have failed to control the disease. Gastrointestinal adverse effects are common on initial treatment and may persist, particularly when very high doses (such as 3 g daily) are given. In order to reduce gastrointestinal effects, treatment should be initiated with a low dose which may be gradually increased. Metformin may provoke lactic acidosis which is most likely to occur in patients with renal impairment; it should not be used in patients with even mild renal impairment. One major advantage of metformin is that it does not usually cause hypoglycaemia. It may be used together with insulin (but weight gain and hypoglycaemia can be problems) or sulfonylureas (but possibility of increased adverse effects with such combinations). During medical and surgical emergencies insulin treatment is almost always required; insulin should be substituted for metformin before elective surgery and in pregnancy.

**GLIBENCLAMIDE**

*Tablets*, glibenclamide 5 mg

**Uses:**
- diabetes mellitus

**Contraindications:**
- ketoacidosis; porphyria; pregnancy (Appendix 2); breastfeeding

ing (Appendix 3)

Precautions:
renal impairment (Appendix 4); hepatic impairment (Appendix 5); elderly; substitute insulin during severe infection, trauma, surgery (see notes above); interactions: Appendix 1

Dosage:
Diabetes mellitus, by mouth, ADULT initially 5 mg once daily with or immediately after breakfast (ELDERLY 2.5 mg, but avoid—see notes above), adjusted according to response (maximum 15 mg daily)

Adverse effects:
mild and infrequent, including gastrointestinal disturbances and headache; liver disorders; hypersensitivity reactions usually in first 6–8 weeks; rarely, erythema multiforme, exfoliative dermatitis, fever and jaundice; hypoglycaemia, particularly in the elderly; rarely blood disorders including leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia

METFORMIN HYDROCHLORIDE

Tablets, metformin hydrochloride 500 mg, 850mg

Uses:
diabetes mellitus (see notes above)

Contraindications:
renal impairment (withdraw if renal impairment suspected; Appendix 4); withdraw if tissue hypoxia likely (for example sepsis, respiratory failure, recent myocardial infarction, hepatic impairment), use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal) and use of general anaesthesia (suspend metformin 2 days beforehand and restart when renal function returns to normal); alcohol dependence; pregnancy (Appendix 2)

Precautions:
measure serum creatinine before treatment and once or twice annually during treatment; substitute insulin during severe infection, trauma, surgery (see notes above and contraindications); breastfeeding (Appendix 3); interactions: Appendix 1

Dosage:
Diabetes mellitus, by mouth, ADULT initially 500 mg with breakfast for at least 1 week then 500 mg with breakfast and evening meal for at least 1 week, then 500 mg with breakfast, lunch and evening meal (maximum 2 g daily in divided doses)

Adverse effects:
anorexia, nausea and vomiting, diarrhoea (usually transient), abdominal pain, metallic taste; lactic acidosis most likely in patients with renal impairment (discontinue); decreased vitamin B₁₂ absorption
18.3.1 Hormonal contraceptives

THYROID HORMONES AND ANTITHYROID DRUGS

Thyroid hormones
Thyroid agents are natural or synthetic agents containing levothyroxine (thyroxine) or liothyronine (tri-iodothyronine). The principal effect is to increase the metabolic rate. They also exert a cardiotimulatory effect which may be the result of a direct action on the heart.

Thyroid hormones are used in hypothyroidism (myxoedema) and also in diffuse non-toxic goitre, Hashimoto thyroiditis (lymphadenoid goitre) and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development.

Levothyroxine sodium (thyroxine sodium) is the treatment of choice for maintenance therapy. It is almost completely absorbed from the gastrointestinal tract but the full effects are not seen for up to 1 to 3 weeks after beginning therapy; there is a slow response to dose change and effects may persist for several weeks after withdrawal. Dosage of levothyroxine in infants and children for congenital hypothyroidism and juvenile myxoedema should be titrated according to clinical response, growth assessment and measurement of plasma thyroxine and thyroid-stimulating hormone.

LEVOTHYROXINE SODIUM

Tablets, levothyroxine sodium 100 micrograms

Uses:
hypothyroidism

Contraindications:
thyrotoxicosis

Precautions:
cardiovascular disorders (myocardial insufficiency or ECG evidence of myocardial infarction); hypopituitarism or predisposition to adrenal insufficiency (must be corrected by corticosteroid prior to initial levothyroxine); elderly; long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (may need to increase dose of insulin or oral antidiabetic drug); pregnancy (Appendix 2), breastfeeding (Appendix 3);

interactions: Appendix 1

Dosage:
Hypothyroidism, by mouth, ADULT initially 50–100 micrograms daily (25–50 micrograms for those over 50 years) before breakfast, increased by 25–50 micrograms every 3–4 weeks until normal metabolism maintained (usual maintenance dose, 100–200 micrograms daily); where there is cardiac disease, initially 25 micrograms daily or 50 micrograms on alternate days, adjusted in steps of 25 micrograms every 4 weeks
Congenital hypothyroidism and juvenile myxoedema (see notes above), by mouth, CHILD up to 1 month, initially 5–10 micro-
grams/kg daily, CHILD over 1 month, initially 5 micrograms/kg daily, adjusted in steps of 25 micrograms every 2–4 weeks, until mild toxic symptoms appear, then reduce dose slightly

**Adverse effects:**
(usually with excessive dose) anginal pain, arrhythmias, palpitations, tachycardia, skeletal muscle cramps, diarrhoea, vomiting, restlessness, excitability, insomnia, headache, flushing, sweating, excessive loss of weight and muscular weakness

**Antithyroid drugs**

Antithyroid drugs such as **propylthiouracil** and carbimazole are used in the management of thyrotoxicosis. They are also used to prepare the patient for thyroidectomy. They are usually well-tolerated, with mild leukopenia or rashes developing in a few percent of cases, usually during the first 6–8 weeks of therapy. During this time the blood count should be checked every 2 weeks or if a sore throat or other signs of infection develop. The drugs are generally given in a high dose in the first instance until the patient becomes euthyroid, the dose may then be gradually reduced to a maintenance dose which is continued for 12–18 months, followed by monitoring to identify relapse. There is a lag time of some 2 weeks between the achievement of biochemical euthyroidism and clinical euthyroidism. Beta-adrenoceptor antagonists (beta-blockers) (usually propranolol) may be used as a short-term adjunct to antithyroid drugs to control symptoms but their use in heart failure associated with thyrotoxicosis is controversial.

Treatment can be given, if necessary, in pregnancy but antithyroid drugs cross the placenta and in high doses may cause fetal goitre and hypothyroidism. The lowest dose that will control the hyperthyroid state should be used (requirements in Graves disease tend to fall during pregnancy). Propylthiouracil appears in breast milk but does not preclude breastfeeding as long as neonatal development is closely monitored and the lowest effective dose is used.

If surgery (partial thyroidectomy) is contemplated, it may be necessary to give iodine for 10 to 14 days in addition to antithyroid drugs to assist control and reduce vascularity of the thyroid. Iodine should not be used for long-term treatment since its antithyroid action tends to diminish. In patients in whom drug therapy fails to achieve long-term remissions definitive treatment with surgery or (increasingly) radioactive iodine is preferable.

**Propylthiouracil**

Propylthiouracil is a representative antithyroid drug. Various drugs can serve as alternatives

18.3.1 Hormonal contraceptives

**Tablets**, propylthiouracil 50 mg

**Uses:**
hyperthyroidism

**Precautions:**
large goitre; pregnancy and breastfeeding (see also notes; Appendices 2 and 3); hepatic impairment (Appendix 5)—withdraw treatment if hepatic function deteriorates (fatal reactions reported); renal impairment—reduce dosage (Appendix 4)

**Dosage:**
Hyperthyroidism, *by mouth*, **ADULT** 300–600 mg daily until patient becomes euthyroid; dose may then be gradually reduced to a maintenance dose of 50–150 mg daily

**Patient Advice.**
Warn patient to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness occurs

**Adverse effects:**
nausea, rashes, pruritus, arthralgia, headache; rarely, alopecia, cutaneous vasculitis, thrombocytopenia, aplastic anaemia, lupus erythematosus-like syndrome, jaundice, hepatitis, hepatic necrosis, encephalopathy, nephritis

**Carbimazole**

**Tablet**, carbimazole 5 mg

**Uses:**
hyperthyroidism

**Cautions:**
liver disorders, pregnancy, breast-feeding

**Dosage:**
carbimazole is given in dose of 15 to 40 mg daily; occasionally a larger dose may be required. This dose is continued until the patient becomes euthyroid, usually after 4 to 8 weeks and the dose is then gradually reduced to a maintenance dose of 5-15 mg. Therapy is usually given for 12-18 months. Children may be given carbimazole in an initial dose of 250 micrograms/kg three times daily, adjusted according to response; treatment in children should be undertaken by a specialist. Rashes and pruritus are common but they can be treated with antihistamines without discontinuing therapy

**Adverse effects:**
nausea, mild gastro-intestinal disturbances, headache, rashes and pruritus, arthralgia: rarely myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis

**Potassium iodide**

**Tablet**, potassium iodide 60 mg

**Uses:**
thyrotoxicosis (pre-operative treatment); sporotrichosis, subcutaneous phlycomycosis (section 6.3)

**Contraindications:**
breastfeeding (Appendix 3); long-term treatment

**Precautions:**
pregnancy (Appendix 2), children

**Dosage:**
ADULT 60–180 mg daily

**Adverse effects:**
hypersensitivity reactions including coryza-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes; on prolonged treatment, depression, insomnia, impotence, goitre in infants of mothers taking iodides
18.3.1 Hormonal contraceptives
SECTION 19: IMMUNOLOGICALS

19.1 Diagnostic agents
19.2 Sera and immunoglobulins
  19.2.1 Anti-D immunoglobulin
  19.2.2 Anti-Tetanus immunoglobulin
  19.2.3 Diptheria antitoxin
  19.2.4 Rbabies immunoglobulin
  19.2.5 Antivenom sera
19.3 Vaccines
  19.3.1 Vaccines for universal immunization
  19.3.2 Vaccines for specific group of individuals
Immunologicals

Active immunity

Active immunity may be induced by the administration of micro-organisms or their products which act as antigens to induce antibodies to confer a protective immune response in the host. Vaccination may consist of (a) a live attenuated form of a virus or bacteria, (b) inactivated preparations of the virus or bacteria, or (c) extracts of or detoxified exotoxins. Live attenuated vaccines usually confer immunity with a single dose which is of long duration. Inactivated vaccines may require a series of injections in the first instance to produce an adequate antibody response and in most cases, require reinforcing (booster) doses. The duration of immunity varies from months to many years. Extracts of or detoxified exotoxins require a primary series of injections followed by reinforcing doses.

Passive immunity

Passive immunity is conferred by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. Treatment has to be given soon after exposure to be effective. This immunity lasts only a few weeks but passive immunization can be repeated where necessary.

19. Diagnostic agents

The tuberculin test has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

Tuberculin purified protein derivative (tuberculin PPD)


Injection, tuberculin purified protein derivative 100 units/ml, 10 units/ml

Uses:
test for hypersensitivity to tuberculoprotein
Contraindications:
should not be used within 3 weeks of receiving a live viral

vaccine

**Precautions:**
elderly; 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

**Dosage:**
Test for hypersensitivity to tuberculoprotein, *by intradermal injection*, **ADULT** and **CHILD** 5 or 10 units (1 unit may be used in hypersensitive patients or if tuberculosis is suspected)

**ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects:**
ocasionally nausea, headache, malaise, rash; immediate local reactions (more common in atopic patients); rarely, vesicular or ulcerating local reactions, regional adenopathy and fever

### 19.2 Sera and immunoglobulins

Antibodies of human origin are usually termed **immunoglobulins.** Material prepared from animals is called **antiserum.** Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced wherever possible by the use of immunoglobulins.

All immunoglobulins and antisera should comply with WHO requirements for blood and plasma products.

**CONTRAINDICATIONS AND PRECAUTIONS**
Anaphylaxis, although rare, can occur and epinephrine (adrenaline) must always be immediately available during immunization.

Immunoglobulins may interfere with the immune response to live virus vaccines which should normally be given *either at least 3 weeks before or at least 3 months after* the administration of the immunoglobulin.

**ADVERSE REACTIONS**
*Intramuscular injection.* Local reactions including pain and tenderness may occur at the injection site. Hypersensitivity reactions may occur including, rarely, anaphylaxis.

*Intravenous injection.* Systemic reactions including fever, chills, facial flushing, headache and nausea may occur, particularly following high rates of infusion. Hypersensitivity reactions may occur including, rarely, anaphylaxis.

### 19.2.1 Anti-D immunoglobulin (human)

**Anti-D immunoglobulin** is prepared from plasma with a high titre of anti-D antibody. It is available to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells which may pass into the maternal circulation. The aim is
to protect any subsequent child from the hazard of haemolytic disease of the newborn. It should be administered following any potentially sensitizing episode (for example abortion, miscarriage, still-birth) immediately or within 72 hours of the episode but even if a longer period has elapsed it may still give protection and should be used. The dose of anti-D immunoglobulin given depends on the level of exposure to rhesus-positive blood. The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. It is also given following Rh₀ (D) incompatible blood.

**Anti-D immunoglobulin (human)**


**Injection**, anti-D immunoglobulin 250-microgram vial

**Uses:**
prevention of formation of antibodies to rhesus-positive blood cells in rhesus-negative patients (see notes above)

**Contraindications:**
see introductory notes; known hypersensitivity

**Precautions:**
see introductory notes; caution in rhesus-positive patients for treatment of blood disorders; caution in rhesus-negative patients with anti-D antibodies in their serum; **interactions:** Appendix 1

**RUBELLA VACCINE.**

Rubella vaccine may be administered in the postpartum period at the same time as anti-D immunoglobulin injection, but only using separate syringes and separate contralateral sites. If blood is transfused, the antibody response to the vaccine may be inhibited and a test for antibodies should be performed after 8 weeks and the subject revaccinated if necessary

**Dosage:**
Following birth of a rhesus-positive infant in rhesus-negative mother, **by intramuscular injection**, ADULT 250 micrograms immediately or within 72 hours (see also notes above)

Following any potentially sensitizing episode (for example amniocentesis, still-birth), **by intramuscular injection**, ADULT up to 20 weeks' gestation, 250 micrograms per episode (after 20 weeks, 500 micrograms) immediately or within 72 hours (see notes above)

Following Rh₀ (D) incompatible blood transfusion, **by intramuscular injection**, ADULT 10–20 micrograms per ml transfused rhesus-positive blood

**Adverse effects:**
see introductory notes

19.2.2 Antitetanus immunoglobulin (human)

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 (see section 19.3.1.2).

Antitetanus immunoglobulin (human)


Injection, antitetanus immunoglobulin 500 units/vial

Uses:
passive immunization against tetanus as part of the management of tetanus-prone wounds

Contraindications:
see introductory notes

Precautions:
see introductory notes

TETANUS VACCINE.

If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites

Dosage:
Management of tetanus-prone wounds, by intramuscular injection, ADULT and CHILD 250 units, increased to 500 units if wound older than 12 hours or there is risk of heavy contamination or if patient weighs more than 90 kg; second dose of 250 units given after 3–4 weeks if patient immunosuppressed or if active immunization with tetanus vaccine contraindicated (see also section 19.3.1.2)

Adverse effects:
see introductory notes

19.2.3 Diphtheria antitoxin

Diphtheria antitoxin is prepared from the plasma or serum of healthy horses immunized against diphtheria toxin or diphtheria toxoid. It is used for passive immunization in suspected cases of diphtheria without waiting for bacterial confirmation of the infection. A test dose should be given initially to exclude hypersensitivity. Diphtheria antitoxin is not used for prophylaxis of diphtheria because of the risk of hypersensitivity.
DIPHTHERIA ANTITOXIN

Injection, diphtheria antitoxin 10 000 units, 20 000 units/ vial

Uses:
passive immunization in suspected cases of diphtheria

Precautions:
initial test dose to exclude hypersensitivity; observation required after full dose (epinephrine (adrenaline) and resuscitation facilities should be available)

Dosage:
Passive immunization in suspected diphtheria (see Precautions), by intramuscular injection, ADULT and CHILD 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)

Adverse effects:
anaphylaxis with urticaria, hypotension, dyspnoea and shock; serum sickness up to 12 days after injection

19.2.4 Rabies immunoglobulin (human)

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 round the site of the bite and also given intramuscularly. In addition rabies vaccine (see section 19.3.2.4) should be administered at a different site.

Rabies immunoglobulin (human)
Injection, rabies immunoglobulin 150 units/ml, 2-ml vial, 10-ml vial

Uses:
passive immunization either post-exposure or in suspected exposure to rabies in high-risk countries in unimmunized individuals (in conjunction with rabies vaccine)

Contraindications:
see introductory notes; avoid repeat doses after vaccine treatment initiated; intravenous administration

**Precautions:**
see introductory notes

**RABIES VACCINE.**
If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites

**Dosage:**
Immunization against rabies: post-exposure (or suspected exposure) treatment, by intramuscular injection and wound infiltration, ADULT and CHILD 20 units/kg (half by intramuscular injection and half by wound infiltration)

**Adverse effects:**
see introductory notes

### 19.2.5 Antivenom sera

Acute envenoming 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, adult respiratory distress syndrome and acute renal failure may occur. Early anaphylactoid symptoms may be treated with epinephrine (adrenaline). **Snake antivenom sera** 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 or severe local involvement or, if supplies are not limited, in patients at high risk of systemic or severe local involvement.

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 sera**, suitable for the species involved, may prevent symptoms if administered as soon as possible after envenomation.

**ANTIVENOM SERA**

*Injection*, snake antivenom serum and spider antivenom serum

**NOTE.**
There are many antivenom sera each containing specific venom-neutralizing globulins. It is important that the specific antivenom serum suitable for the species causing the envenomation is administered

**Uses:**
treatment of snake bites and spider bites

**Precautions:**
resuscitation facilities should be immediately available

**Dosage:**
Depends on the specific antivenom used; consult manufacturer’s literature

**Adverse effects:**
serum sickness; anaphylaxis with hypotension, dyspnoea, urticaria and shock

### 19.3 Vaccines

All vaccines should comply with the WHO requirements for biological substances. Vaccines may consist of a live attenuated form of a virus (for example, rubella or measles) or bacteria (for example, BCG vaccine); an inactivated preparation of a virus (for example, influenza vaccine) or bacteria; an extract of or detoxified exotoxin produced by a micro-organism (for example, tetanus vaccine).

**CONTRAINDICATIONS AND PRECAUTIONS**

Recipients of any vaccine should be observed for an adverse reaction. Anaphylaxis though rare, can occur and epinephrine (adrenaline) must always be immediately available whenever immunization is given. If a serious adverse event (including anaphylaxis, collapse, shock, encephalitis, encephalopathy, or non-febrile convulsion) occurs following a dose of any vaccine, a subsequent dose should not be given. In the case of a severe reaction to Diphtheria, Pertussis, and Tetanus vaccine, the pertussis component should be omitted and the vaccination completed with Diphtheria and Tetanus vaccine. Immunization should be postponed in acute illness which may limit the response to immunization, but minor infections without fever or systemic upset are not contraindications. A definite reaction to a preceding dose is a definite contraindication. If alcohol or other disinfecting agent is used to wipe the injection site it must be allowed to evaporate, otherwise inactivation of a live vaccine may occur.

The intramuscular route must not be used in patients with bleeding disorders such as haemophilia or thrombocytopenia. Some viral vaccines contain small quantities of antibacterials such as polymyxin B or neomycin; such vaccines may need to be withheld from individuals who are extremely sensitive to the antibacterial. Some vaccines are prepared using Belize Drug Formulary and Therapeutics Manual Ninth Edition 2009-2011
hens’ eggs and a history of anaphylaxis to egg ingestion is a contraindication to the use of such vaccines; caution is required if such vaccines are used in persons with less severe hypersensitivity to egg. When two live virus vaccines are required (and are not available as a combined preparation) they should be given *either* simultaneously at different sites using separate syringes or with an interval of at least 3 weeks. Live virus vaccines should normally be given *either at least 2–3 weeks before or at least 3 months after* the administration of immunoglobulin. Live vaccines should not be routinely administered to pregnant women because of the possible harm to the fetus but where there is significant risk of exposure, the need for immunization may outweigh any possible risk to the fetus. Live vaccines should not be given to anyone with malignant disease such as leukaemia or lymphomas or other tumours of the reticulo-endothelial system. Live vaccines should not be given to individuals with an impaired immune response caused by disease, radiotherapy or drug treatment (for example, high doses of corticosteroids). However, the WHO recommends that immunocompromised individuals who are HIV-positive should, under certain circumstances, be given some live vaccines. *Asymptomatic* and *symptomatic* HIV-positive children and women of child-bearing age should receive diphtheria, pertussis, tetanus, hepatitis B and oral poliomyelitis vaccines (included in the Expanded Programme on Immunization (EPI)). Because of the risk of early and severe measles infection, infants should receive an extra dose of measles vaccine at 6 months of age with the EPI dose as soon after 9 months of age as possible. Individuals with *symptomatic* HIV infection must not be given either BCG or yellow fever vaccines. MMR vaccine should not be given to severely immunocompromised children with HIV infection. Individuals with *asymptomatic* HIV infection should only be given BCG or yellow fever vaccines where the prevalence of tuberculosis or yellow fever, respectively, is high. National policies on immunization of HIV-positive individuals may vary.

**ADVERSE REACTIONS**

Local reactions including inflammation and lymphangitis may occur. Sterile abscess may develop at the injection site; fever, headache, malaise starting a few hours after injection and lasting for 1–2 days may occur. Hypersensitivity reactions can occur including rarely, anaphylaxis.

**19.3.1 Vaccines for universal immunization**

**The WHO Expanded Programme on Immunization (EPI)**

19.3.1 Vaccines for universal immunization

Currently recommends that all countries immunize against diphtheria, hepatitis B, measles, poliomyelitis, pertussis, tetanus and that countries with a high incidence of tuberculosis infections should immunize against tuberculosis. Immunization against yellow fever is recommended in endemic countries. Routine vaccination against *Haemophilus influenzae* type b infection is also recommended in some countries. In geographical regions where the burden of disease is unclear, efforts should be made to evaluate the magnitude of the problem.

**Immunization schedule recommended by WHO**

**Scheme A**
Recommended in countries where perinatal transmission of hepatitis B virus is frequent (for example, countries in south-east Asia)

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>BCG; Poliomyelitis, oral (1st); Hepatitis B (1st)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>Diphtheria, pertussis, tetanus (1st); <em>Haemophilus influenzae</em> (type b)(^1) (1st); Poliomyelitis, oral (2nd); Hepatitis B (2nd)</td>
</tr>
<tr>
<td>10 weeks</td>
<td>Diphtheria, pertussis, tetanus (2nd); <em>Haemophilus influenzae</em> (type b)(^1) (2nd); Poliomyelitis, oral (3rd)</td>
</tr>
<tr>
<td>14 weeks</td>
<td>Diphtheria, pertussis, tetanus (3rd); <em>Haemophilus influenzae</em> (type b)(^1) (3rd); Poliomyelitis, oral (4th); Hepatitis B (3rd)</td>
</tr>
<tr>
<td>9 months</td>
<td>Yellow fever (in countries where yellow fever poses a risk); Measles</td>
</tr>
</tbody>
</table>

**Scheme B**
Recommended in countries where perinatal transmission of hepatitis B virus is less frequent (for example, countries in sub-Saharan Africa)

Schedule as Scheme A, but hepatitis B (1st) given at 6 weeks and hepatitis B (2nd) given at 10 weeks

\(^1\) *Haemophilus influenzae* (type b) vaccine not included on WHO Model List

**BCG vaccine (dried)**

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*), is highly cost-effective. This has been estimated, in several settings, to reduce the incidence of meningeal and miliary tuberculosis in early childhood by 50 to 90%. However, estimates of its effectiveness in older children have differed greatly from region to region and because efficacy against pulmonary tuberculosis is doubtful, the mainstay of the tuberculosis control programme is case-finding and treatment.

**BCG VACCINE**


*Injection (Powder for solution for injection), live bacteria of a strain derived from the bacillus of Calmette and Guérin*

**Uses:**
active immunization against tuberculosis; see also section 6.2.4

**Contraindications:**
see introductory notes; generalized oedema; antimycobacterial treatment

**Precautions:**
pregnancy (Appendix 2); eczema, scabies—vaccine site must be lesion-free; **interactions:** Appendix 1

**Dosage:**
Immunization against tuberculosis, by *intradermal injection*,
**INFANTS** up to 3 months, 0.05 ml; **ADULT** and **CHILD** over 3 months, 0.1 ml

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects:**
see introductory notes; lymphadenitis and keloid formation; osteitis and localized necrotic ulceration; rarely, disseminated BCG infection in immunodeficient patients; rarely anaphylaxis

**Diphtheria, pertussis and tetanus vaccines**

**DIPHTHERIA**

Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*, 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. Immunized individuals can be infected by toxin-producing strains of diphtheria but systemic manifestations of the disease do not occur. When administered for primary immunization in infants, diphtheria vaccine is almost always given together with pertussis and tetanus vaccines as part of a three-component preparation (DPT).

A two-component diphtheria vaccine with tetanus but without pertussis exists in two forms, DT and Td. Diphtheria-tetanus vaccine for children (DT) is used for primary immunization in infants who have contraindications to pertussis vaccine; it is also used in children under the age of 10 years for reinforcing immunization against diphtheria and tetanus in those countries which recommend it. Tetanus-diphtheria vaccine for adults, adolescents and children over 10 years of age (Td), which has a reduced amount of diphtheria toxoid to reduce the risk of hypersensitivity reactions, is used for primary immunization in persons over the age of 10 years; it is also used for reinforcing immunization in persons over the age of 10 years in those countries that recommend it.

PERTUSSIS

Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordetella pertussis*. Many of the symptoms are thought to be caused by toxins released by *B. pertussis*. Whole cell vaccine composed of whole pertussis bacteria killed by chemicals or heat is effective in preventing serious illness. It causes frequent local reactions and fever and rarely it may be associated with neurological reactions. Neurological complications after pertussis infection are considerably more common than after the vaccine. It is combined with diphtheria-tetanus vaccine for primary immunization unless immunization against pertussis is contraindicated. Single component pertussis vaccines are available in some countries for use when the pertussis component has been omitted from all or part of the primary immunization schedule. An acellular form of the vaccine is also available.

In some countries it is recommended that children with a personal or family history of febrile convulsions or a family history of idiopathic epilepsy should be immunized. It is also recommended that children with well-controlled epilepsy are immunized. Advice on prevention of fever should be given at the time of immunization. In children with evolving neurological problems, immunization with pertussis should be deferred until the condition is stable; in such children diphtheria and tetanus vaccine should be offered for primary immunization, and there may be an opportunity at a later date to complete immunization with a single-component pertussis vaccine. Where there is doubt advice should be sought from a paediatrician.
TETANUS

Tetanus is caused by the action of a neurotoxin of *Clostridium tetani* in necrosed tissues such as occur in dirty wounds. Tetanus vaccine is available as a single component vaccine for primary immunization in adults who have not received childhood immunization against tetanus and for reinforcing immunization. The vaccine is also used in the prevention of neonatal tetanus and in the management of clean wounds and tetanus-prone wounds. Some countries recommend a maximum of 5 doses of tetanus vaccine in a life-time; for the fully immunized patient reinforcing doses at the time of a tetanus-prone injury should only be required if more than 10 years have elapsed since the last dose.

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. Tetanus vaccine is highly effective and the efficacy of two doses during pregnancy in preventing neonatal tetanus ranges from 80–100%. Women of child-bearing age may be immunized by a course of 5 doses (3 primary and 2 reinforcing) of tetanus vaccine.

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 significant degree of devitalized tissue, clinical evidence of sepsis, contamination with soil/manure likely to contain tetanus organisms. All wounds should receive thorough surgical toilet. Antibacterial prophylaxis may also be required for tetanus-prone wounds.

- For *clean wounds*, fully immunized individuals (those who have received a total of 5 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 whose immunization status is not known) should be given a dose of the vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).

- For *tetanus-prone wounds*, management is as for clean wounds with the addition of a dose of antitetanus immunoglobulin (section 19.2.2) given at a different site; in fully immunized individuals and those whose primary immunization is complete
19.3.1 Vaccines for universal immunization

(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.

Diphtheria, pertussis, and tetanus vaccine (DPT)

DPT vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 800, 1990

Injection, diphtheria and tetanus toxoids and pertussis vaccine adsorbed onto a mineral carrier

Uses:
active immunization against diphtheria, tetanus and pertussis

Contraindications:
see introductory notes and notes above

Precautions:
see introductory notes and notes above; in cases of severe reaction, the pertussis component should be omitted and the primary course of immunization completed with diphtheria and tetanus vaccine

Dosage:
Primary immunization of children against diphtheria, pertussis and tetanus, by intramuscular injection, INFANT 0.5 ml at 6, 10 and 14 weeks (see WHO schedule, section 19.3.1)

Adverse effects:
see introductory notes; tetanus component rarely associated with peripheral neuropathy; pertussis component rarely associated with convulsions and encephalopathy

Diphtheria and tetanus vaccine (DT) (for children under 10 years)

DT vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 800, 1990

Injection, diphtheria and tetanus toxoids adsorbed onto a mineral carrier

Uses:
active immunization of children under 10 years against diphtheria and tetanus (see notes above)

Contraindications:
see introductory notes; adults and children over 10 years of age (see notes above)

Precautions:
see introductory notes

**Dosage:**

**NOTE.**

National immunization schedules may vary

Primary immunization of children against diphtheria and tetanus when pertussis immunization is contraindicated, by intramuscular injection, **CHILD** under 10 years 3 doses each of 0.5 ml with an interval of not less than 4 weeks between each dose (see also WHO schedule, section 19.3.1)

Reinforcing immunization of children against diphtheria and tetanus, by intramuscular injection, **CHILD** under 10 years of age, 0.5 ml at least 3 years after completion of primary course of DPT or DT immunization

**Adverse effects:**

see introductory notes; tetanus component rarely associated with peripheral neuropathy

**Tetanus and diphtheria vaccine (Td) (for adults, adolescents and children over 10 years)**

Td vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 800, 1990

**Injection**, diphtheria (low dose) and tetanus toxoid adsorbed onto a mineral carrier

**Uses:**

active immunization of adults and children over 10 years of age against tetanus and diphtheria (see notes above)

**Contraindications:**

see introductory notes; children under 10 years (see notes above)

**Precautions:**

see introductory notes

**Dosage:**

Primary immunization of unimmunized adults and children over 10 years of age against tetanus and diphtheria, by intramuscular injection, **ADULT** and **CHILD** over 10 years of age, 3 doses each of 0.5 ml with an interval of not less than 4 weeks between each dose

Reinforcing immunization of adults and children over 10 years of age against tetanus and diphtheria, by intramuscular injection, **ADULT** and **CHILD** over 10 years of age, 0.5 ml 10 years after completing primary course

**Adverse effects:**

see introductory notes; tetanus component rarely associated with peripheral neuropathy

19.3.1 Vaccines for universal immunization

**Tetanus vaccine**

Tetanus vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 800, 1990

*Injection*, tetanus toxoid adsorbed onto a mineral carrier

**Uses:**
active immunization against tetanus and neonatal tetanus; wound management (tetanus-prone wounds and clean wounds)

**Contraindications:**
see introductory notes and notes above

**Precautions:**
see introductory notes and notes above

**ANTITETANUS IMMUNOGLOBULIN.**
If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites

**Dosage:**

*NOTE.*
National immunization schedules may vary; some countries recommend a **maximum** of 5 doses of tetanus vaccine in a life-time

Primary immunization of unimmunized adults against tetanus, *by intramuscular injection*, **ADULT** 3 doses each of 0.5 ml with an interval of 4 weeks between each dose

Reinforcing immunization of adults against tetanus, *by intramuscular injection*, **ADULT** 2 doses each of 0.5 ml, the first 10 years after completion of primary course, and the second dose 10 years later

Immunization of women of child-bearing age against tetanus, *by intramuscular injection*, **woman of child-bearing age**, 3 primary doses each of 0.5 ml with an interval of not less than 4 weeks between the first and second doses and 6 months between the second and third doses; 2 reinforcing doses each of 0.5 ml, the first 1 year after completion of the primary course and the second dose 1 year later; **unimmunized pregnant woman** 2 doses of 0.5 ml with an interval of 4 weeks between each dose (second dose at least 2 weeks before delivery) and 1 dose during each of subsequent 3 pregnancies (maximum 5 doses)

Management of tetanus-prone wounds and clean wounds, *by intramuscular or deep subcutaneous injection*, **ADULT** 0.5 ml, the dose schedule being dependent upon the immune status of the patient and the level of contamination of the wound (see also notes above and under Antitetanus Immunoglobulin, section 19.2.2)

Adverse effects:
see introductory notes; tetanus component rarely associated with peripheral neuropathy

Hepatitis B vaccine

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 life-style, occupation or other factors include parenteral drug abusers, individuals who change sexual partners frequently, health care workers who are at risk of injury from blood-stained sharp instruments and haemophiliacs. Also at risk are babies born to mothers who are HbsAg-positive (hepatitis B virus surface antigen positive) and individuals who might acquire the infection as the result of medical or dental procedures in countries of high prevalence. The main public health consequences are chronic liver disease and liver cancer rather than acute infection. Routine immunization is recommended and has been implemented in some countries. Plasma-derived hepatitis B vaccine is highly efficacious. Over 90% of susceptible children develop a protective antibody response. A recombinant DNA vaccine is also available.

Hepatitis B vaccine

Hepatitis B vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 858, 1995

Injection, inactivated hepatitis B surface antigen adsorbed onto a mineral carrier

Uses:
active immunization against hepatitis B

Contraindications:
see introductory notes

Precautions:
see introductory notes

Dosage:
Immunization of children against hepatitis B, by intramuscular injection, INFANT 0.5 ml either Scheme A at birth and at 6 and 14 weeks of age, or Scheme B at 6, 10 and 14 weeks of age (see WHO schedule, section 19.3.1)
Immunization of unimmunized high risk persons against hepatitis B, by intramuscular injection, ADULT and CHILD over 15 years of age, 3 doses of 1 ml, with an interval of 1 month between the first and second dose and 5 months between the second and third doses; CHILD under 15 years, 0.5 ml
NOTE.
Different products may contain different concentrations of antigen. Consult manufacturer’s literature

ADMINISTRATION.
The vaccine should be given in the deltoid region in adults and older children; anterolateral thigh is the preferred site in infants and young children; it should not be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for patients with thrombocytopenia or bleeding disorders

Adverse effects:
see introductory notes; abdominal pain and gastrointestinal disturbances; muscle and joint pain, dizziness and sleep disturbance; occasionally cardiovascular effects

Hepatitis C

Measles vaccines

Measles is an acute viral infection transmitted by close respiratory contact. In some countries routine immunization of children against measles is given as one dose of a single component vaccine; in other areas, a two-dose schedule has been found to be more applicable. In developing countries, clinical efficacy is usually greater than 85%. Convulsions and encephalitis are rare complications. Measles vaccine is administered in many countries as part of a combined preparation with mumps vaccine and rubella vaccine (MMR vaccine); a single-dose primary immunization is followed by a reinforcing dose 2–5 years later.

Single-component vaccines or MMR may be used in the control of outbreaks of measles and should be offered to susceptible children within 3 days of exposure. It is important to note that MMR vaccine is not suitable for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

MEASLES VACCINE


Injection (Powder for solution for injection), live, attenuated measles virus

Uses:
active immunization against measles

Contraindications:
see introductory notes; hypersensitivity to any antibiotic present in vaccine—consult manufacturer’s literature; hypersensitivity

to egg or gelatin

**Precautions:**
see introductory notes; pregnancy (Appendix 2); **interactions:** Appendix 1

**Dosage:**
Immunization of children against measles, *by intramuscular or deep subcutaneous injection*, INFANT at 9 months of age, 0.5 ml (see WHO schedule, section 19.3.1) Prophylaxis in susceptible children after exposure to measles, *by intramuscular or deep subcutaneous injection* within 72 hours of contact, CHILD over 9 months of age 0.5 ml

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects:**
see introductory notes; rashes sometimes accompanied by convulsions; rarely, encephalitis and thrombocytopenia

**MEASLES, MUMPS AND RUBELLA VACCINE (MMR VACCINE)**


**Injection**, live, attenuated measles virus, mumps virus and rubella virus

**Uses:**
active immunization against measles, mumps and rubella

**Contraindications:**
see introductory notes; pregnancy (Appendix 2); hypersensitivity to any antibiotic present in vaccine—consult manufacturer’s literature; hypersensitivity to egg

**Precautions:**
see introductory notes; history of convulsions—advice on controlling fever (see below); **interactions:** Appendix 1

**POST-IMMUNIZATION FEVER.**
Malaise, fever or rash may occur following the first dose of MMR vaccine, most commonly about 1 week after immunization and lasting 2–3 days. Carers should be advised that the child can be given paracetamol to reduce the fever followed if necessary by a second dose 4–6 hours later. If fever persists after the second dose of paracetamol, medical advice should be sought. After a second dose of MMR vaccine, adverse reactions are considerably less common than after the first dose

**Dosage:**
Primary immunization of children against measles, mumps and rubella, *by intramuscular or deep subcutaneous injection*, CHILD 12–15 months, 0.5 ml

Reinforcing immunization of children against measles, mumps

and rubella, *by intramuscular or deep subcutaneous injection*, CHILD 0.5 ml 2–5 years after primary dose

Prophylaxis in susceptible children after exposure to measles (see notes above), *by intramuscular or deep subcutaneous injection* within 72 hours of contact, CHILD 12 months of age and older, 0.5 ml

**Adverse effects:**
see introductory notes; malaise, fever, rash most common after first dose (see above); occasionally parotid swelling; rarely meningoencephalitis, idiopathic thrombocytopenic purpura

### Poliomyelitis vaccines

Poliomyelitis is an acute viral infection spread by the faecal-oral route which can cause paralysis of varying degree. There are two types of vaccine against poliomyelitis: oral and injectable. Oral poliomyelitis vaccine (OPV) is composed of three types of live attenuated poliomyelitis viruses. The efficacy of OPV in preventing paralytic polio in developing countries ranges from 72% to 98% and is the vaccine of choice in eradication of the disease. Oral poliomyelitis vaccine may need to be repeated in patients with diarrhoea or vomiting. Those infected with HIV should receive poliomyelitis vaccine according to the standard schedule but the vaccine is **contraindicated** in those with primary immune deficiency or those who are immunosuppressed. 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 particularly of the need to wash their hands after changing the baby’s nappies. After primary immunization reinforcing doses may be given. Inactivated polio vaccine (IPV) is injectable and composed of inactivated strains of three types of poliomyelitis virus. It should be used for individuals who are immunosuppressed or for their household contacts.

**POLIOMYELITIS VACCINE (OPV) (LIVE ATTENUATED)**

OPV should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 800, 1990

*Oral suspension*, live, attenuated poliomyelitis virus, types 1, 2, and 3

**Uses:**
active immunization against poliomyelitis

**Contraindications:**
see introductory notes; primary immunodeficiency or immunosuppression; not to be taken with food which contains a preservative; hypersensitivity to any antibiotic present in vaccine—consult manufacturer’s literature

**Precautions:**
see introductory notes; pregnancy (Appendix 2); interactions: Appendix 1

**Dosage:**
Primary immunization of children against poliomyelitis, by mouth, CHILD 3 drops at birth and at 6, 10 and at 14 weeks of age (see WHO schedule, section 19.3.1)
Reinforcing immunization of children against poliomyelitis, by mouth, CHILD 3 drops at least 3 years after completion of primary course and a further 3 drops at 15–19 years of age
Primary immunization of unimmunized adult against poliomyelitis, by mouth, ADULT 3 doses each of 3 drops with an interval of at least 4 weeks between each dose
Reinforcing immunization of adults against poliomyelitis, by mouth, ADULT 3 drops 10 years after completion of primary course

**NOTE.**
Some countries consider reinforcing immunization unnecessary in adults unless travelling to endemic areas

**Adverse effects:**
rarely, vaccine-associated poliomyelitis in recipients of vaccine and contacts of recipients

**POLIOMYELITIS VACCINE (IPV) (INACTIVATED)**

IPV should comply with the recommendations published in the reports of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 673, 1982 and Addendum 1985, WHO Technical Report Series, No. 745, 1987 Injection, inactivated poliomyelitis virus, types 1, 2, and 3

**Uses:**
active immunization against poliomyelitis in patients for whom live vaccine is contraindicated (see notes above) or in persons in countries not wishing to use live vaccine

**Contraindications:**
see introductory notes

**Precautions:**
see introductory notes

**Dosage:**
Primary immunization of children against poliomyelitis, by subcutaneous injection, child 0.5 ml at 6, 10 and 14 weeks of age
Reinforcing immunization of children against poliomyelitis, by subcutaneous (or intramuscular) injection, child 0.5 ml at least 3 years after completion of the primary course and a further 0.5 ml at 15–19 years of age
Primary immunization of unimmunized adults against poliomyelitis, by subcutaneous injection, ADULT 3 doses each of 0.5 ml with intervals of at least 4 weeks between each dose
Reinforcing immunization of adults against poliomyelitis, by subcutaneous injection, **ADULT** 0.5 ml 10 years after completion of primary course

**NOTE.**
Some countries consider reinforcing immunization unnecessary in adults unless travelling to endemic areas

**Adverse effects:**
see introductory notes

**19.3.2 Vaccines for specific groups of individuals**

There are several other vaccines available which are used in different countries but are not yet recommended for routine use throughout the world.

**Influenza vaccine**

While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly changing their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that **influenza vaccines** in use contain the H and N components of the prevalent strain or strains. The changes are monitored and recommendations are made each year regarding the strains to be included in influenza vaccines for the following season. The recommended vaccine strains are grown on chick embryos and the vaccine is therefore contraindicated in individuals hypersensitive to egg. There are three forms of influenza vaccine; whole virion vaccine (not recommended for use in children because of the increased risk of severe febrile reactions), split-virion vaccine and surface-antigen vaccine. The vaccines will not control epidemics and they are recommended only for those at high risk. Annual immunization is recommended in the elderly and those of any age with diabetes mellitus, chronic heart disease, chronic renal failure, chronic respiratory disease including asthma, or immunosuppression due to disease or drug treatment.

**INFLUENZA VACCINE**

Influenza vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 814, 1991

**Injection**, inactivated influenza virus, types A and B

**Uses:**
active immunization against influenza in individuals at risk

**Contraindications:**
see introductory notes; whole virion vaccine not recommended in children; hypersensitivity to any antibiotic present in vaccine—consult manufacturer’s literature; hypersensitivity to egg

Precautions:
see introductory notes; interactions: Appendix 1

Dosage:
Immunization against influenza (annually for high-risk persons), by intramuscular or deep subcutaneous injection, ADULT and CHILD over 13 years, 0.5 ml as a single dose; CHILD 6–35 months, 0.25 ml repeated after at least 4 weeks if child not previously infected or vaccinated; CHILD 3–12 years of age, 0.5 ml, with a second dose after at least 4 weeks if child not previously infected or vaccinated

Adverse effects:
see introductory notes; occasionally, severe febrile reactions—particularly after whole virion vaccine in children

Meningococcal polysaccharide vaccine

*Meningococcal polysaccharide vaccine* is effective against serogroups A and C of *Neisseria meningitidis* but infants respond less well than adults. Immunity to some meningococcal vaccines may be insufficient to confer adequate protection against infection in infants under about 2 years of age and the minimum age recommended by manufacturers varies from 2 months to 2 years. It is indicated for persons at risk of serogroups A and C meningococcal disease in epidemics (where it must be administered early in the course of the epidemic) or endemic areas and as an adjunct to chemoprophylaxis in close contacts of persons with the disease. It is indicated for visits of longer than 1 month to areas of the world where risk of infection is high.

**MENINGOCOCCAL POLYSACCHARIDE VACCINE**


*Injection* (Powder for solution for injection), inactivated polysaccharide antigens of *Neisseria meningitidis* (meningococcus) groups A and C

*Uses:*
Active immunization against meningitis and septicaemia caused by *N. meningitidis* group A and C serotypes

*Contraindications:*
19.3.2 Vaccines for specific groups of individuals

see introductory notes

Precautions:
see introductory notes

Dosage:
Immunization against infection by *N. meningitidis* groups A and C, *by deep subcutaneous or by intramuscular injection*, ADULT and CHILD (see notes above and manufacturer’s literature), 0.5 ml as a single dose

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer’s directions

Adverse effects:
see introductory notes

Mumps vaccine is used for active immunization against mumps. In some countries the single antigen vaccine is no longer available and a combined measles, mumps and rubella vaccine (MMR vaccine; section 19.3.1.4) is used for primary immunization.

**MUMPS VACCINE**

Mumps vaccine should comply with the recommendations published in the reports of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 840, 1994 and No. 848, 1994

*Injection* (Powder for solution for injection), live attenuated strain of mumps virus

Uses:
active immunization against mumps

Contraindications:
see introductory notes; pregnancy (Appendix 2); hypersensitivity to any antibacterial present in the vaccine—consult manufacturer’s literature; hypersensitivity to egg

Precautions:
see introductory notes; avoid in children under 1 year

Dosage:
Immunization of children against mumps, *by subcutaneous injection*, child over 1 year 0.5 ml

**RECONSTITUTION AND ADMINISTRATION.**
According to manufacturer’s directions

Adverse effects:
parotid swelling; rarely, unilateral nerve deafness, meningitis, encephalitis

Rabies vaccine (inactivated)

**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. 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 may be indicated (see Rabies Immunoglobulin, section 19.2.4). Treatment should also include thorough wound cleansing. The vaccine is also used for pre-exposure prophylaxis against rabies in those at high risk such as laboratory workers, veterinary surgeons, animal handlers and health workers who are likely to come into close contact with infected animals or patients with rabies. Pre-exposure prophylaxis is also recommended for those living or travelling in enzootic areas who may be exposed to unusual risk.

RABIES VACCINE (INACTIVATED) (PREPARED IN CELL CULTURE)


Injection, inactivated rabies virus prepared in cell culture

Uses:
Active immunization against rabies; pre-exposure prophylaxis, post-exposure treatment (see notes above)

Contraindications:
see introductory notes

Precautions:
see introductory notes

RABIES IMMUNOGLOBULIN.

If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites

Dosage:
Immunization against rabies: pre-exposure prophylaxis, by deep subcutaneous or by intramuscular injection, ADULT and CHILD 1 ml on days 0, 7 and 28, with reinforcing doses every 2–3 years for those at continued risk
Immunization against rabies: post-exposure treatment (in unimmunized individuals), by deep subcutaneous or by intramuscular injection, ADULT and CHILD 5 doses of 1 ml on days 0, 3, 7, 14 and 28 (plus rabies immunoglobulin given on day 0, section 19.2.4; see notes above)
Immunization against rabies: post-exposure treatment (in fully immunized individuals), by deep subcutaneous or by intramuscular injection, adult and child 2 doses of 1 ml separated by 3–7 days (see notes above)
Adverse effects:
see introductory notes; pain, erythema and induration at injection site; nausea, myalgia; hypersensitivity—less likely with vaccines from human sources

Rubella vaccine

Rubella vaccine should be given to women of child-bearing age if they are seronegative to protect them from the risks of rubella in pregnancy. It should not be given in pregnancy and patients should be advised not to become pregnant within one month of vaccination. However, congenital rubella syndrome has not been reported following inadvertent immunization shortly before or during pregnancy. There is no evidence that the vaccine is teratogenic and routine termination of pregnancy following inadvertent immunization should not be recommended. There is no risk to a pregnant woman from contact with recently vaccinated persons as the vaccine virus is not transmitted.

The vaccine may contain traces of antibiotics and if so should not be used in individuals with hypersensitivity to them.

In some countries the policy of protecting women of childbearing age has been replaced by a policy of eliminating rubella in children. Rubella vaccine is a component of the MMR vaccine (see section 19.3.1.4). Countries seeking to eliminate rubella should ensure that women of child-bearing age are immune and that over 80% of children are immunized.

RUBELLA VACCINE


Uses:
active immunization against rubella in women of child-bearing age

Contraindications:
see introductory notes; pregnancy (see notes above); hypersensitivity to any antibiotic present in vaccine—consult manufacturer’s literature; hypersensitivity to egg

Precautions:
see introductory notes; interactions: Appendix 1

Dosage:
Immunization of women of child-bearing age against rubella,
by deep subcutaneous or by intramuscular injection, adult, 0.5 ml as a single dose

**RECONSTITUTION AND ADMINISTRATION.**

According to the manufacturer’s directions

**Adverse effects:**

see introductory notes; rash, lymphadenopathy; arthralgia and arthritis; rarely, thrombocytopenia, neurological symptoms

**Typhoid vaccine**

**Typhoid vaccine** is used for active immunization against typhoid fever and immunization is advised for those travelling to endemic areas. The efficacy of the vaccine is not complete and the importance of maintaining scrupulous attention to food and water hygiene as well as personal hygiene must also be emphasized.

Typhoid vaccine is available as a capsular polysaccharide injection.

In children under 2 years the injection may show sub-optimal response. Immunization is also recommended for laboratory workers handling specimens from suspected cases.

A live oral typhoid vaccine containing an attenuated strain of *Salmonella typhi* (Ty21a) may also be available.

**TYPHOID VACCINE**

Typhoid vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 840, 1994

*Capsule*, live attenuated strain of *Salmonella typhi* (Ty21a)

*Injection*, Vi capsular polysaccharide typhoid 25 microgram/0.5 ml

**Uses:**

active immunization against typhoid

**Contraindications:**

see introductory notes

**Precautions:**

see introductory notes and notes above

**Dosage:**

Immunization against typhoid fever, by mouth, ADULT and CHILD over 6 years, one dose given on days 0, 2, and 4 (total of 3 doses), with reinforcing doses every year for travellers to disease-endemic countries and every 3 years for those living in disease-endemic areas

Immunization against typhoid fever, by deep subcutaneous or by intramuscular injection, ADULT and CHILD (see notes above) 0.5 ml, with reinforcing doses every 3 years for those
19.3.2 Vaccines for specific groups of individuals

at continued risk

ADMINISTRATION.
According to the manufacturer’s directions
Adverse effects:
see introductory notes

Yellow fever vaccine

Yellow fever is a viral haemorrhagic fever endemic in some countries of South America and Africa. The disease is transmitted by *Haemagogus* and *Aedes* mosquito bites. The vaccine is highly immunogenic and offers about 10 years protection. Over 92% of children develop protective antibodies. It is recommended that all countries in which yellow fever is endemic should incorporate this vaccine into their immunization schedule. It is also used for travellers to endemic areas.

YELLOW FEVER VACCINE

Yellow fever vaccine should comply with the recommendations published in the reports of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 872, 1998

*Injection* (Powder for solution for injection), live, attenuated yellow fever virus

Uses:
active immunization against yellow fever

Contraindications:
see introductory notes; not recommended for infants under 6 months of age; hypersensitivity to any antibiotic present in vaccine—consult manufacturer’s literature; hypersensitivity to egg

Precautions:
see introductory notes; pregnancy (Appendix 2); interactions: Appendix 1

Dosage:
Immunization of children against yellow fever, by *subcutaneous injection*, INFANT at 9 months of age, 0.5 ml (see WHO schedule, section 19.3.1)

Immunization of travellers and others at risk against yellow fever, by *subcutaneous injection*, ADULT and CHILD over 9 months of age 0.5 ml; INFANT 6–9 months of age 0.5 ml, only if risk of yellow fever is unavoidable (see Adverse Effects)

RECONSTITUTION AND ADMINISTRATION.
According to manufacturer’s directions
Adverse effects:
see introductory notes; rarely encephalitis, generally in infants under 9 months
19.3.2 Vaccines for specific groups of individuals
Section 20: Muscle relaxants (peripherally acting) and cholinesterase inhibitors

20.1 Muscle relaxants
20.2 Cholinesterase Inhibitors
20.1 Muscle relaxants

Muscle relaxants

Muscle relaxants used in surgery include suxamethonium; for further details see section 1.4.

20.2 Cholinesterase inhibitors

MYASTHENIA GRAVIS

Cholinesterase inhibitors, such as neostigmine and pyridostigmine, are used in the symptomatic treatment of myasthenia gravis. They act by inhibiting acetylcholinesterase, thereby prolonging the action of acetylcholine, and thus enhancing neuromuscular transmission; this produces at least a partial improvement in most myasthenic patients but complete restoration of muscle strength is rare. Unless the patient has difficulty in swallowing, cholinesterase inhibitors are given by mouth. Pyridostigmine has a slower onset (usually within 30–60 minutes), but a longer duration of effect than neostigmine; it also tends to cause fewer muscarinic effects such as diarrhoea, abdominal cramps, and excess salivation, so is usually preferred. Doses should be carefully adjusted to avoid precipitating a cholinergic crisis due to overdosage; this must be differentiated from a myasthenic crisis due to disease progression, and consequent underdosage; the principal effect in both cases is increased muscle weakness.

In myasthenic crisis, if the patient has difficulty in breathing and in swallowing, the cholinesterase inhibitor must be given by intramuscular or subcutaneous injection; neostigmine is usually preferred. To reduce muscarinic effects, atropine (section 1.3) should also be given.

For the use of neostigmine in surgery, see section 1.4.

A corticosteroid such as prednisolone (section 18.1), is used for the treatment of myasthenia gravis; addition of azathioprine (section 8.1) may allow a dose reduction of both the corticosteroid and of the anticholinesterase.

Neostigmine

Tablets, neostigmine bromide 15 mg

Injection (Solution for injection), neostigmine metilsulfate 500 micrograms/ml, 1-ml ampoule; 2.5 mg/ml, 1-ml ampoule

Uses:

Myasthenia gravis; reversal of non-depolarizing block, postoperative urinary retention (section 1.4)

Contraindications:

recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis

**Precautions:**
asthma; urinary tract infections; cardiovascular disease including arrhythmias (especially bradycardia, vagotonia, recent myocardial infarction or atroventricular block); hyperthyroidism; hypotension; peptic ulcer; epilepsy; parkinsonism; renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

**Dosage:**
Myasthenia gravis, *by mouth* as neostigmine bromide, **ADULT** initially 15–30 mg at suitable intervals throughout the day, gradually increased until desired response obtained, total daily dose within range 75–300 mg, taken at appropriate intervals when maximum strength required, but doses above 180 mg daily not usually tolerated; **CHILD** up to 6 years, initially 7.5 mg, 6–12 years, initially 15 mg, total daily dose usually 15–90 mg in divided doses at appropriate intervals

Myasthenia gravis, *by subcutaneous or intramuscular injection* as neostigmine metilsulfate, **ADULT** 0.5–2.5 mg as required, total daily dose 5–20 mg; **NEONATE** 50–250 micrograms 30 minutes before feeds (not usually required beyond 8 weeks of age); **CHILD** 200–500 micrograms as required

**Adverse effects:**
increased salivation, nausea and vomiting, abdominal cramps, diarrhoea; signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis; thrombophlebitis reported; rash associated with bromide salt

**PYRIDOSTIGMINE BROMIDE**
Pyridostigmine bromide is a complementary cholinesterase inhibitor

*Tablets*, pyridostigmine bromide 60 mg

*Injection* (Solution for injection), pyridostigmine bromide 1 mg/ml, 1-ml ampoule

**Uses:**
Myasthenia gravis

**Contraindications:**
recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis

**Precautions:**
asthma; urinary tract infection; cardiovascular disease includ-
ing arrhythmias (especially bradycardia or atrioventricular block); hyperthyroidism; hypotension; peptic ulcer; epilepsy; parkinsonism; avoid intravenous injection; renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); interactions: Appendix 1

Dosage:
Myasthenia gravis, by mouth, ADULT initially 30–120 mg at suitable intervals throughout the day, gradually increased until desired response obtained; total daily dose within range 0.3–1.2 g, taken at appropriate intervals when maximum strength required, but doses above 450 mg daily not usually advisable in order to avoid acetylcholine receptor downregulation; CHILD up to 6 years initially 30 mg, 6–12 years initially 60 mg; total daily dose usually 30–360 mg in divided doses at appropriate intervals.

Myasthenia gravis, by intramuscular injection, ADULT 2 mg every 2–3 hours; neonate 50–150 micrograms before feeds (but neostigmine usually preferred); CHILD, total daily dose 1–12 mg given in divided doses at appropriate intervals.

Adverse effects:
muscarinic effects generally weaker than with neostigmine: increased salivation, nausea and vomiting, abdominal cramps, diarrhoea; signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis; thrombophlebitis; rash associated with bromide salt.
SECTION 21:
OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents
21.2 Anti-inflammatory agents
21.3 Local anaesthetics
21.4 Antiglaucoma medicines
  21.4.1 Miotics
  21.4.2 Beta-blockers
  21.4.3 Sympathomimetics
  21.4.4 Carbonic anhydrase inhibitors
21.5 Mydriatics and cycloplegics
**Administration of eye preparations**

Preparations for the eye should be sterile when issued. Use of single-application containers is preferable; multiple-application preparations include antimicrobial preservatives and when used particular care should be taken to prevent contamination of the contents, including the avoidance of contact between the applicator and the eye or other surfaces.

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, dilution and overflow may occur when one immediately follows the other; an interval of 5 minutes should be allowed between the two applications.

Systemic absorption, which may occur after topical application of eye drops, can be minimized by using the finger to compress the lacrimal sac at the medial canthus for at least one minute after instillation of the drops. This helps block the passage of the drops through the naso-lacrimal duct.

**PERFORMANCE OF SKILLED TASKS**

Application of eye preparations may cause blurring of vision which is generally transient; patients should be advised not to carry out skilled tasks such as operating machinery or driving until their vision has cleared.

**21.1 Anti-infective drugs**

Blepharitis, conjunctivitis, keratitis and endophthalmitis are common acute infections of the eye and can be treated topically. However, in some cases, for example, in gonococcal conjunctivitis, both topical and systemic anti-infective treatment may be necessary. Blepharitis and conjunctivitis are often caused by staphylococcus, while keratitis and endophthalmitis may be bacterial, viral or fungal. Bacterial blepharitis is treated with an antibacterial eye ointment or drops. Although most cases of acute bacterial conjunctivitis may resolve spontaneously, anti-infective treatment shortens the infectious process and prevents complications. Acute infective conjunctivitis is treated with antibacterial eye drops by day and eye ointment applied at night. A poor response may indicate viral or allergic conjunctivitis. Keratitis requires immediate specialist treatment.

**Gentamicin** is a broad-spectrum bactericidal aminoglycoside
antibiotic with particular activity against *Pseudomonas aeruginosa*, *Neisseria gonorrhoea* and other bacteria that may be implicated in blepharitis or conjunctivitis. Topical application may lead to systemic absorption and possible adverse effects. **Tetracycline** is a broad spectrum antibiotic with activity against many Gram-positive and Gram-negative bacteria including *N. gonorrhoea*, and most chlamydia, rickettsia, mycoplasma and spirochetes. Ophthalmic tetracycline is used in blepharitis, conjunctivitis, and keratitis produced by susceptible bacteria. Tetracycline is also used in the treatment of trachoma caused by *Chlamydia trachomatis* and in the prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) caused by *N. gonorrhoea* and *C. trachomatis*.

**Chloramphenicol**, is a potent broad spectrum antibiotic. Chloramphenicol see section( ).

**GENTAMICIN**

Gentamicin is a representative antibacterial. Various drugs can serve as alternatives

*Eye drops, solution, gentamicin (as sulfate) 0.3%*

**Uses:**

blepharitis; bacterial conjunctivitis; systemic infections (section 6.2.2.5)

**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

**Administration:**

Mild to moderate infection, by *instillation into the eye*, ADULT and CHILD 1 drop every 2 hours, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete

Severe infection, by *instillation into the eye*, ADULT and CHILD 1 drop every hour, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete

**Adverse effects:**

burning, stinging, itching, dermatitis

**TETRACYCLINE HYDROCHLORIDE**

Tetracycline is a representative antibacterial. Various drugs can serve as alternatives

*Eye ointment, tetracycline hydrochloride 1%*

**Uses:**

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

**Precautions:**
prolonged use may lead to overgrowth of non-susceptible organisms

**Administration:**
Superficial bacterial infection, *by application to the eye*, **ADULT** and **CHILD** aged over 8 years 1 application of ointment 3–4 times daily

Prophylaxis of neonatal conjunctivitis, *by application to the eye*, **NEWBORN** at birth after cleansing eyes with sterile gauze, 1 application of ointment into each eye; close eyelids and massage gently to aid spread of ointment

Trachoma, intermittent treatment, *by application to the eye*, **ADULT** and **CHILD** 1 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, *by application to the eye*, **ADULT** and **CHILD** 1 application of ointment into each eye twice daily for at least 6 weeks

**Adverse effects:**
rash; rarely stinging, burning

**CHLORAMPHENICOL**

Eye drops, 0.5%
Ointment, 1%

**Use**
Active against superficial eye infection

**Adverse effect**
Transient stinging

**Administration**
Eye drops. Apply 1 drop at least every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing

Eye ointment. Apply either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment is used alone

**Preparation**
Chloramphenicol + prednisone; *solution*, 2.5+ 5mg/ml

**CIPROFLOXACIN**

Otic drops, ciprofloxacin 0.2% + Hydrocortisone1%, 10ml

**Use**
Acute otitis media externa, sometimes know as swimmer’s ear

**Precaution**
Not recommended to children under 1 year, pregnancy and breastfeeding

**Adverse effects**
Local burning and itching, hyperaemia; taste disturbance

**Administration**
Three drops of the suspension in the infected ear twice a day for seven days

21.2

**Anti-inflammatory drugs**

Ophthalmic corticosteroids should only be used under supervision of an ophthalmologist as inappropriate use is potentially blinding. Dangers include the development of open-angle glaucoma (chronic simple glaucoma) and cataracts, and the aggravation of a simple herpes simplex epithelial lesion into an extensive corneal ulcer and subsequent permanent corneal scarring, with possible damage to vision and even loss of the eye.

Corticosteroids such as **prednisolone** are useful in the treatment of inflammatory conditions including uveitis and scleritis. They are also used for reducing postoperative ocular inflammation. Before administration of an ophthalmic corticosteroid, the possibility of bacterial, viral or fungal infection should be excluded. Treatment should be the lowest effective dose for the shortest possible time; if long-term therapy (more than 6 weeks) is unavoidable, withdrawal of an ophthalmic corticosteroid should be gradual to avoid relapse.

**PREDNISOLONE SODIUM PHOSPHATE**

Prednisolone is a representative corticosteroid. Various drugs can serve as alternatives

*Eye drops, solution*, prednisolone sodium phosphate 0.5%

**Uses:**
short-term local treatment of inflammation of the eye; malignant disease (section 8.3); inflammatory and allergic reactions (section 18.1, also section 3.1)

**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

**Administration:**

**NOTE.**

Use only under the supervision of an ophthalmologist
Inflammation of the eye, by instillation into the eye. ADULT and CHILD 1 drop every 1–2 hours, reducing frequency as inflammation is controlled

**Adverse effects:**
secondary ocular infection; impaired corneal healing (due to corneal thinning), optic nerve damage, cataract; glaucoma, mydriasis, ptosis, epithelial punctate keratitis, delayed hypersensitivity reactions including burning, stinging

**HYDROCORTISONE**

Ophtalmic ointment, 1%

**Use**
Local treatment of inflammation

**Adverse effects**
Steroid glaucoma, steroid cataract, thinning of the corneal

**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

**Preparation**
Otosporin ®- Hydrocortisone1%+ neomycin sulphate 3400units, polymixin B sulphate 10000 units/ml- Ear drop (otic)

**21.3 Local anaesthetics**

Topical local anaesthetics are employed for simple ophthalmological procedures and for short operative procedures involving the cornea and conjunctiva. **Tetracaine**, available in 0.5% ophthalmic solution, provides a rapid local anaesthesia which lasts for 15 minutes or more. Prolonged or unsupervised use of tetracaine is not recommended.

**TETRACAINE HYDROCHLORIDE**

Amethocaine

Tetracaine is a representative local anaesthetic. Various drugs can serve as alternatives

**Eye drops, solution**, tetracaine hydrochloride 0.5%

**Uses:**
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
21.4 Antiglaucoma drugs

Glaucoma is normally associated with raised intra-ocular pressure and eventual damage to the optic nerve which may result in blindness. The rise in pressure is almost always due to reduced outflow of aqueous humour, the inflow remaining constant. The most common condition is chronic open-angle glaucoma (chronic simple glaucoma) in which the intra-ocular pressure increases gradually and the condition is usually asymptomatic until well advanced. In contrast, angle-closure glaucoma (closed-angle glaucoma) usually occurs as an acute emergency resulting from a rapid rise in intra-ocular pressure; if treatment is delayed, chronic angle-closure glaucoma may develop. Ocular hypertension is a condition in which intra-ocular pressure is raised without signs of optic nerve damage.

Drugs used in the treatment of glaucoma lower the intra-ocular pressure by a variety of mechanisms including reduction in secretion of aqueous humour by the ciliary body, or increasing the outflow of the aqueous humour by opening of the trabecular network. Antiglaucoma drugs used include topical application of a beta-blocker (beta-adrenoceptor antagonist), a miotic, or a sympathomimetic such as epinephrine; systemic administration of a carbonic anhydrase inhibitor may be used as an adjunct.

Timolol is a non-selective beta-blocker that reduces the secretion of aqueous humour. A beta-blocker is usually the drug of choice for initial and maintenance treatment of chronic open-angle glaucoma. If further reduction in intra-ocular pressure is required a miotic, a sympathomimetic or a systemic carbonic anhydrase inhibitor may be used with timolol. In angle-closure glaucoma, timolol should be used with a miotic and not alone.

A miotic such as pilocarpine, through its parasympathomimetic action, contracts the iris sphincter muscle and the ciliary muscle, and opens the trabecular network. It is used in chronic open-angle glaucoma either alone or, if required, with a beta-blocker, epinephrine or a systemic carbonic anhydrase inhibitor. Pilocarpine is used with systemic acetazolamide in an acute attack of angle-closure glaucoma prior to surgery; however,
it is not advisable to use pilocarpine after surgery because of a risk of posterior synechiae forming. Systemic absorption of topically applied pilocarpine can occur producing muscarinic adverse effects.

**Acetazolamide**, by reducing carbonic anhydrase in the eye, reduces the production of aqueous humour and so reduces intra-ocular pressure. It is used systemically as an adjunct in chronic open-angle glaucoma unresponsive to treatment with topically applied antiglaucoma drugs. Prolonged therapy with acetazolamide is not normally recommended, but if treatment is unavoidable blood count and plasma electrolyte concentration should be monitored. Acetazolamide is also used as part of emergency treatment for an acute attack of angle-closure glaucoma; however it should not be used in chronic angle-closure glaucoma as it may mask deterioration of the condition.

### 21.4.1 Miotics

**Pilocarpine**

Pilocarpine is a representative miotic. Various drugs can serve as alternatives

*Eye drops, solution*, pilocarpine hydrochloride 2%, 4%; pilocarpine nitrate 2%, 4%

**Uses:**
chronic open-angle glaucoma, ocular hypertension; emergency treatment of acute angle-closure glaucoma; to antagonize effects of mydriasis and cycloplegia following surgery or ophthalmoscopic examination

**Contraindications:**
acute iritis, acute uveitis, anterior uveitis, some forms of secondary glaucoma; acute inflammation of anterior segment; not advisable after angle-closure surgery (risk of posterior synechiae)

**Precautions:**
retinal disease, conjunctival or corneal damage; monitor intra-ocular pressure in chronic open-angle glaucoma and in long-term treatment; cardiac disease, hypertension, asthma, peptic ulceration, urinary-tract obstruction, Parkinson disease; stop treatment if symptoms of systemic toxicity develop

**PatientAdvice.**
Causes difficulty with dark adaptation; may cause accommodation spasm. Do not carry out skilled tasks, for example operating machinery or driving until vision is clear

**Administration:**
Chronic open-angle glaucoma, by instillation into the eye, **ADULT** 1 drop (2% or 4%) up to 4 times daily
Acute angle-closure glaucoma before surgery, by instillation into the eye, **ADULT** 1 drop (2%) every 10 minutes for 30–60 minutes, then 1 drop every 1–3 hours until intra-ocular pres-
sure subsides

**Adverse effects:**
- eye pain, blurred vision, ciliary spasm, lacrimation, myopia, browache; conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage and increased pupillary block have been reported; lens opacities have occurred following prolonged use; rarely systemic effects including hypertension, tachycardia, bronchial spasm, pulmonary oedema, salivation, sweating, nausea, vomiting, diarrhoea

### 21.4.2 Beta-blockers

**Timolol**

Timolol is a representative beta-blocker. Various drugs can serve as alternatives

*Eye drops, solution*, timolol (as maleate) 0.25%, 0.5%

**Uses:**
- ocular hypertension; chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas

**Contraindications:**
- uncontrolled heart failure, bradycardia, heart block; asthma, obstructive airways disease

**Precautions:**
- older people (risk of keratitis); if used in angle-closure glaucoma, use with a miotic, and not alone; **interactions**: Appendix 1

**Administration:**

Ocular hypertension, chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas, *by instillation into the eye*, ADULT 1 drop (0.25% or 0.5%) twice daily

**Adverse effects:**
- stinging, burning, pain, itching, erythema, transient dryness, allergic blepharitis, transient conjunctivitis, keratitis, decreased corneal sensitivity, diplopia, ptosis; systemic effects, particularly on the pulmonary, cardiovascular and central nervous systems, may follow absorption

**BETAXALOL**

Ophthalmic, 0.50%

**Use**
- ocular hypertension; chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas

**Contraindications:**
- uncontrolled heart failure, bradycardia, heart block; asthma, obstructive airways disease

**Precautions:**
- older people (risk of keratitis); if used in angle-closure glaucoma, use with a miotic, and not alone; **interactions**: Appendix 1
Administration:
Ocular hypertension, chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas, **by instillation into the eye**, ADULT 1 drop (0.25% or 0.5%) twice daily

21.4.4 Carbonic anhydrase inhibitors

**ACETAZOLAMIDE**

*Tablets, acetazolamide 250 mg*

**Uses:**
as an adjunct in the treatment of chronic open-angle glaucoma; secondary glaucoma; as part of pre-operative treatment of acute angle-closure glaucoma

**Contraindications:**
hypersensitivity to sulfonamides; chronic angle-closure glaucoma (may mask deterioration); hypokalaemia, hyponatraemia, hyperchloraemic acidosis; renal impairment (Appendix 4), severe hepatic impairment

**Precautions:**
elderly; pregnancy (Appendix 2); breastfeeding (Appendix 3); diabetes mellitus; pulmonary obstruction; monitor blood count and electrolytes if used for long periods; **interactions:** Appendix 1

**PatientAdvice**
May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage:**
Chronic open-angle glaucoma, secondary glaucoma, **by mouth**, ADULT 0.25–1 g daily in divided doses

**Adverse effects:**
nausea, vomiting, diarrhoea, taste disturbance; loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression; thirst, polyuria; reduced libido; metabolic acidosis and electrolyte disturbances on long-term therapy; occasionally drowsiness, confusion, hearing disturbances, urticaria, melaena, glycosuria, haematuria, abnormal liver function, renal calculi, blood disorders including agranulocytosis and thrombocytopenia, rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis; transient myopia reported

21.5 Mydriatics and cycloplegics

Antimuscarinics, by blocking the cholinergic effects of acetylcholine, paralyse the pupillary constrictor muscles causing dilation of the pupil (mydriasis) and paralyse the ciliary muscles resulting in paralysis of accommodation (cycloplegia). Mydriasis may precipitate acute angle-closure glaucoma particularly in
elderly or long-sighted patients. In patients with dark iridic pig-
mentation, higher concentrations of mydriatic drugs are usually
required and care should be taken to avoid overdosing.

**Atropine** is a long-acting antimuscarinic used for cycloplegic
refraction procedures, particularly in children. It is also used to
immobilize the ciliary muscle and iris and to prevent formation
of posterior synechiae in the treatment of inflammatory eye
disorders such as iritis and uveitis. **Cyclopentolate** is also used
to produce cyclopegia for refraction in young children.

**Atropine sulfate**

*Eye drops, solution*, atropine sulfate 0.1%, 0.5%, 1%

**Uses:**
- iritis, uveitis; cycloplegic refraction procedures; premedication
  (section 1.3); organophosphate poisoning (section 4.2.3);
  antispasmodic (section 17.5)

**Contraindications:**
- Angle-closure glaucoma

**Precautions:**
- May precipitate acute attack of angle-closure glaucoma,
  particularly in the elderly or long-sighted; risk of systemic ef-
  fects with eye drops in infants under 3 months—eye ointment
  preferred

**PatientAdvice.**
- May cause sensitivity to light and blurred vision. Do not carry
  out skilled tasks, for example operating machinery or driving,
  until vision is clear

**Administration:**
- Cycloplegic refraction, *by instillation into the eye*, **ADULT** 1
drop (1%) twice daily for 1–2 days before procedure or a single
  application of 1 drop (1%) 1 hour before procedure; **CHILD**
  under 3 months (see Precautions), 3 months–1 year (0.1%),
  1–5 years (0.1–0.5%), over 5 years (0.5–1%), 1 drop twice
daily for 1–3 days before procedure with a further dose given
  1 hour before procedure
- Iritis, uveitis, *by instillation into the eye*, **ADULT** 1 drop (0.5
  or 1%) up to 4 times daily; **CHILD** 1 drop (0.5 or 1%) up to 3
times daily

**Adverse effects:**
- transient stinging and raised intra-ocular pressure; on pro-
  longed administration, local irritation, hyperaemia, oedema and
  conjunctivitis may occur; contact dermatitis; systemic toxicity
  may occur in the very young and the elderly

**CYCLOPENTOLATE**

**Opthalmic drops, 0.5 %, 10ml**

**Use**
Facilitate examination of the fundus of the eyes in children

**Caution**
Mydriasis may precipitate acute angle- closure glaucoma in a very few patients, usually age over 60 and hypermetropic (long sighted) who are predisposed to the condition because of a shallow anterior chamber.

**Adverse effects:**
Ocular side effects of mydriatics and cycloplegics include transient stinging and raised intra-ocular pressure; on prolonged administration, local irritation, hyperaemia, oedema and conjunctivitis may occur; contact dermatitis; systemic toxicity may occur in the very young and the elderly

**Administration:**
Cycloplegic refraction, *by instillation into the eye*, **ADULT** 1 drop (1%) twice daily for 1–2 days before procedure or a single application of 1 drop (1%) 1 hour before procedure; **CHILD** under 3 months (see Precautions), 3 months–1 year (0.1%), 1–5 years (0.1–0.5%), over 5 years (0.5–1%), 1 drop twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure

Iritis, uveitis, *by instillation into the eye*, **ADULT** 1 drop (0.5 or 1%) up to 4 times daily; **CHILD** 1 drop (0.5 or 1%) up to 3 times daily

**Homatropine**

Opthalmic drop, 2%

**Use**
Used in the treatment of anterior segment inflammation, to produce cycloplegia and mydriasis for retraction

**Precaution**
Use with caution in patients with hypertension, cardiac disease, or increased intraocular pressure

**Contraindication**
Angle-closure glaucoma

**Adverse effects**
Blurred vision, photophobia, increased intra ocular pressure

**Dosage**
**CHILDREN**, Mydriasis and cyclopegia for refraction: instill 1 drop 2% immediately before the procedure, repeat at 10 mins intervals as needed

Uvetis: Instill 1 drop of 2% solution 2-3 times a day

**ADULTS**, Mydriasis and cyclopegia for refraction: instill 1-2 drops 2% immediately before the procedure, repeat at 5-10 mins intervals as needed, max. Of 3 doses for refraction

Uvetis: Instill 1-2 drops of 2% solution 3-4 hours as needed

Antivirals

Herpes simplex infection producing, for example dendritic corneal ulcer can be treated with *acyclovir*

**ACYCLOVIR**

Ophthalmic drops, 3%

**Use**
Local treatment of Herpes simplex infection

**Adverse effects**
Local inflammation and irritation

**Administration**
Apply 5 times a day

ENT-Topical nasal decongestants

Symptoms of nasal congestion associated with vasomotor rhinitis and the common cold can be relieved by the short term use (usually no longer than seven days) of decongestion nasal drops and spray. These all contain sympathomimetic drugs which exert their effects by vasoconstriction on the mucosal blood vessel which in turn reduces oedema of the nasal mucosa.

**Oxymetazoline**

Nasal drops, 0.5%, 10ml

**Use**
Adjunctive therapy of middle ear infections, associated with acute or chronic rhinitis, the common cold, sinusitis, hay fever, or other allergies

**Contraindications**
Hypersensitivity to oxymetazoline or any component of the formulation

**Precautions**
Rebound congestion may occur with extended use (>3 days).

**Adverse effects**
Hypertension, palpitation, transient burning, stinging, dryness of the nasal mucosa, rebound congestion with prolonged use, sneezing

**Dosage**
Intranasal (therapy should not exceed 3 days): **CHILDREN**
6 years and **ADULTS**: 0.05% solution: Instill 2-3 sprays into each nostril twice daily
SECTION 22:
DRUGS USED IN OBSTETRICS

22.1 Drugs used in obstetrics
22.1 Drugs used in obstetrics

Drugs may be used to modify uterine contractions. These include oxytocic drugs used to stimulate uterine contractions both in induction of labour and to control postpartum haemorrhage and beta$_2$-adrenoceptor agonists used to relax the uterus and prevent premature labour.

POSTPARTUM HAEMORRHAGE

Ergometrine and oxytocin differ in their actions on the uterus. In moderate doses oxytocin produces slow generalized contractions with full relaxation in between; ergometrine produces faster contractions superimposed on a tonic contraction. High doses of both substances produce sustained tonic contractions. Oxytocin is now recommended for routine use in postpartum and post-abortion haemorrhage since it is more stable than ergometrine. However, ergometrine may be used if oxytocin is not available or in emergency situations.

PREMATURE LABOUR

Salbutamol is a beta$_2$-adrenoceptor agonist which relaxes the uterus and can be used to prevent premature labour in uncomplicated cases between 24 and 33 weeks of gestation. Its main purpose is to permit a delay in delivery of at least 48 hours. The greatest benefit is obtained by using this delay to administer corticosteroid therapy or to implement other measures known to improve perinatal health. Prolonged therapy should be avoided since the risks to the mother increase after 48 hours and the response of the myometrium is reduced.

ECLAMPSIA AND PRE-ECLAMPSIA

Magnesium sulfate has a major role in eclampsia for the prevention of recurrent seizures. Monitoring of blood pressure, respiratory rate and urinary output is carried out, as is monitoring for clinical signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, double vision and slurred speech—calcium gluconate injection (section 27.2) is used for the management of magnesium toxicity). Magnesium sulfate is also used in women with pre-eclampsia who are at risk of developing eclampsia; careful monitoring of the patient (as described above) is necessary.

Ergometrine maleate

Ergometrine is subject to international control under the United
Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988)

Ergometrine is a representative oxytocic drug. Various drugs can serve as alternatives

*Tablets*, ergometrine maleate 200 micrograms

*Injection* (Solution for injection), ergometrine maleate 200 micrograms/ml, 1-ml ampoule

**NOTE.**

Injection requires transport by ‘cold chain’ and refrigerated storage

**Uses:**

prevention and treatment of postpartum and post-abortion haemorrhage in emergency situations and where oxytocin not available

**Contraindications:**

induction of labour, first and second stages of labour; vascular disease, severe cardiac disease especially angina pectoris; severe hypertension; severe renal and hepatic impairment; sepsis; eclampsia

**Precautions:**

cardiac disease, hypertension, hepatic impairment (Appendix 5) and renal failure (Appendix 4), multiple pregnancy, porphyria;

**Interactions:** Appendix 1

**Dosage:**

Prevention and treatment of postpartum haemorrhage, when oxytocin is not available, *by intramuscular injection, ADULT* and *adolescent* 200 micrograms when the anterior shoulder is delivered or immediately after birth

Excessive uterine bleeding, *by slow intravenous injection, ADULT* and *adolescent* 250–500 micrograms when the anterior shoulder is delivered or immediately after birth

Secondary postpartum haemorrhage, *by mouth, ADULT* and *adolescent* 400 micrograms 3 times daily for 3 days

**Adverse effects:**

nausea, vomiting, headache, dizziness, tinnitus, abdominal pain, chest pain, palpitations, dyspnoea, bradycardia, transient hypertension, vasoconstriction; stroke, myocardial infarction and pulmonary oedema also reported

**MAGNESIUM SULFATE**

*Injection* (Solution for injection), magnesium sulfate 500 mg/ml, 2-ml ampoule, 10-ml ampoule

**Uses:**

prevention of recurrent seizures in eclampsia; prevention of seizures in pre-eclampsia

**Precautions:**

Hepatic impairment (Appendix 5); renal failure (Appendix 4); in severe hypomagnesaemia administer initially via a controlled

infusion device; **interactions:** Appendix 1

**Dosage:**
Prevention of recurrent seizures in eclampsia, *by intravenous injection*, **ADULT** and **adolescent** initially 4 g over 5–15 minutes followed *either by intravenous infusion*, 1 g/hour for at least 24 hours after the last seizure or *by deep intramuscular injection* 5 g into each buttock then 5 g every 4 hours into alternate buttocks for at least 24 hours after the last seizure; recurrence of seizures may require additional *intravenous injection* of 2 g

Prevention of seizures in pre-eclampsia, *by intravenous infusion*, **adult** and **adolescent** initially 4 g over 5–15 minutes followed *either by intravenous infusion*, 1 g/hour for 24 hours or *by deep intramuscular injection* 5 g into each buttock then 5 g every 4 hours into alternate buttocks for 24 hours; if seizure occurs, additional dose *by intravenous injection* of 2 g

**DILUTION AND ADMINISTRATION.**
According to manufacturer’s directions *For intravenous injection* concentration of magnesium sulfate should not exceed 20% (dilute 1 part of magnesium sulfate injection 50% with at least 1.5 parts of water for injection); *for intramuscular injection*, mix magnesium sulfate injection 50% with 1 ml lidocaine injection 2%

**Adverse effects:**
generally associated with hypermagnesaemia (see also notes above), nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, muscle weakness; see also Appendix 2

**OXYTOCIN**

*Injection* (Solution for injection), oxytocin 10 units/ml, 1-ml ampoule

**Uses:**
Routine prevention and treatment of postpartum and post-abortion haemorrhage; induction of labour

**Contraindications:**
Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-resistant uterine inertia, in severe pre-eclamptic toxaemia or in severe cardiovascular disease

**Precautions:**
induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant); mild to moderate pregnancy-associated hypertension or cardiac disease; age over 35 years; history of low-uterine segment caesarean section; avoid tumultuous labour if fetal death or meconium-

stained amniotic fluid (risk of amniotic fluid embolism); water intoxication and hyponatraemia (avoid large volume infusions and restrict fluid intake); caudal block anaesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics); **interactions:** Appendix 1

**Dosage:**

Induction of labour, *by intravenous infusion*, **ADULT** and **adolescent**, initially 0.001–0.002 units/minute increased in 0.001–0.002 units/minute increments at intervals of 30 minutes until a maximum of 3–4 contractions occur every 10 minutes; maximum recommended rate 0.02 units/minute; no more than 5 units should be administered in 24 hours

**NOTE.**
The dose shown above is suitable for use in hospital where equipment to control the infusion rate is available; alternative recommendations may be suitable for other settings (consult *Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors 2003*. Geneva: WHO)

**IMPORTANT.**
Careful monitoring of fetal heart rate and uterine motility essential for dose titration (never give intravenous bolus injection during labour); discontinue immediately in uterine hyperactivity or fetal distress

Prevention of postpartum haemorrhage, *by slow intravenous injection*, **ADULT** and **adolescent** 5 units when the anterior shoulder is delivered or immediately after birth

Prevention of postpartum haemorrhage, *by intramuscular injection*, **adult** and **adolescent** 10 units when the anterior shoulder is delivered or immediately after birth

Treatment of postpartum haemorrhage, *by slow intravenous injection*, **adult** and **adolescent** 5–10 units or *by intramuscular injection*, 10 units, followed in severe cases *by intravenous infusion*, a total of 40 units should be infused at a rate of 0.02–0.04 units/minute; this should be started after the placenta is delivered

**DILUTION AND ADMINISTRATION.**
According to manufacturer’s directions. Prolonged intravenous administration at high doses with large volume of fluid (for example in inevitable or missed abortion or postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid: use electrolyte-containing diluent (not glucose), increase oxytocin concentration to reduce fluid, restrict fluid intake by mouth; monitor fluid and electrolytes

**Adverse effects:**
Uterine spasm, uterine hyperstimulation (usually with excessive doses)—may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture); water intoxication and hyponatraemia associated with high doses and large-volume infusions; nausea,
vomiting, arrhythmias, rashes and anaphylactoid reactions also reported

**RITODRINE**

Injection, 10mg/ml, 5ml amp  
**Use**  
Uncomplicated premature labour  
**Precaution**  
Suspicious cardiac disease, hypertension, hyperthyroidism, hypokalemia, diabetes mellitus, mild to moderate preclampsia, monitor blood pressure and heart rate (should not exceed 140 beats per minute), and avoid over hydration; concomitant beta-blocker treatment; drug likely to enhance sympathomimetic side-effects or induce arrhythmias  
**Contraindications**  
Cardiac disease, eclampsia, intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage, placenta praevia cord compression  
**Adverse effects**  
Nausea, vomiting, flushing, sweating, tremor, hypokalemia, tachycardia, palpitations, and hypotension (left lateral position throughout infusion to minimize risk), uterine bleeding (may be reversed with a non-selective beta-blocker); pulmonary oedema; chest pain and tightness and arrhythmias (have been reported); saliva gland enlargement; on prolonged administration (several weeks), leucopenia and agranulocytosis; liver function abnormalities reported.  
**Dosage**  
By intravenous infusion: initially 50 micrograms/minute, increased gradually according to response by 50 micrograms/minute every 10 minutes until contractions stop or maternal heart rate reaches 140 beats per minutes, continue for 12-48 hours after contraction cease (usual rate 150-350 micrograms/minute), max. rate 350 mcg/min; or by intramuscular injection, 10 mg every 3-8 hours continue for 12-48 hours after contraction have ceased, then by mouth, 10 mg 30 min before termination of intravenous infusion, repeat every 2 hours for 24 hours, followed by 10-20 mg every 4-6 hours, max. Oral dose 120mg daily
SECTION 23: PERITONEAL DIALYSIS SOLUTION

23.1 Peritoneal dialysis solution
23.1 Peritoneal dialysis solution

Solutions for peritoneal dialysis are preparations for intraperitoneal use which contain electrolytes in a similar concentration to that in plasma, and also contain glucose or another suitable osmotic agent. Peritoneal dialysis solutions always contain sodium, chloride, and hydrogen carbonate or a precursor; they may also contain calcium, magnesium, and potassium.

In renal failure haemodialysis is the preferred method to correct the accumulation of toxins, electrolytes and fluid. Peritoneal dialysis is less efficient than haemodialysis, but it is preferred in children, diabetic patients, and patients with unstable cardiovascular disease; it is also used in patients who can manage their condition, or those who live far from a dialysis centre. It is unsuitable for patients who have had significant abdominal surgery.

In peritoneal dialysis, the solution is infused into the peritoneal cavity, where exchange of electrolytes takes place by diffusion and convection, and excess fluid is removed by osmosis, 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, again because of poor technique. With long-term dialysis progressive structural changes to the peritoneal membrane occur, ultimately resulting in dialysis failure.

**PERITONEAL DIALYSIS SOLUTION**

Peritoneal dialysis solution is a complementary preparation

*Dialysis solution* (Solution for peritoneal dialysis), intraperitoneal dialysis solution of appropriate composition

**Uses:**
To correct electrolyte imbalance and fluid overload, and to remove metabolites, in renal failure

**Contraindications:**
Abdominal sepsis; previous abdominal surgery; severe inflammatory bowel disease

**Precautions:**

23.1 Peritoneal dialysis solution

Care required with technique to reduce risk of infection; warm dialysis solution to body temperature before use; some drugs may be removed by dialysis

**Dosage:**
Individualized according to clinical condition, and based on blood results

**Adverse effects:**
Infection, including peritonitis; hernia; haemoperitoneum; hyperglycaemia, protein malnutrition; blocked catheter
SECTION 24: 
Psychotherapeutic drugs

24.1 Medicines used in psychotic disorders
24.2 Medicines used in mood disorders
24.2.1 Medicines used in depressive disorders
24.3 Medicines used in generalized anxiety and sleep disorders
24.4 Medicines used for obsessive compulsive disorder and panic attacks
24.1 Drugs used in psychotic disorders

Treatment of psychotic disorders is both pharmacological and psychosocial. Individual and community programmes for relearning old skills and developing new ones and for learning to cope with the illness should be initiated. Classes of antipsychotic drugs include phenothiazines (for example chlorpromazine), butyrophenones (for example haloperidol), thioxanthenes (for example flupentixol) and newer ‘atypical’ neuroleptics including clozapine, quetiapine and risperidone. The various antipsychotic drugs do not, in general, differ in their antipsychotic activity, but differ in range and quality of adverse effects (see below).

ACUTE PHASE TREATMENT

The administration of chlorpromazine or haloperidol will relieve symptoms such as thought disorder, hallucinations and delusions and prevent relapse. They are usually less effective in apathetic, withdrawn patients. However, haloperidol may restore an acutely ill schizophrenic, who was previously withdrawn, or even mute and akinetic, to normal activity and social behaviour. In the acute phase chlorpromazine may be administered by intramuscular injection in a dose of 25–50 mg which can be repeated every 6–8 hours while observing the patient for possible hypotension. In most cases, however, the intramuscular injection is not needed and patients can be treated with an oral dose. Haloperidol may be administered in the acute phase.

MAINTENANCE THERAPY

Long-term treatment in patients with a definite diagnosis of schizophrenia may be necessary after the first episode to prevent the manifest illness from becoming chronic. The lowest possible dose of antipsychotic drug that will prevent major exacerbations of florid symptoms is used for long-term management. Too rapid a dose reduction should be avoided. Intramuscular depot preparations such as fluphenazine decanoate may be used as an alternative to oral maintenance therapy especially when compliance with oral treatment is unreliable. Exacerbations of illness in patients on maintenance drug therapy can be precipitated by stress. Withdrawal of maintenance drug treatment requires careful surveillance since it is not possible to predict the course of the disease and the patient may suffer a relapse if treatment is withdrawn inappropriately. Further, the need for continuation of treatment may not be evident on withdrawal of treatment because relapse may be delayed for several weeks.
ADVERSE EFFECTS
They are very common with long-term administration of antipsychotic medicines. Hypotension and interference with temperature regulation, neuroleptic malignant syndrome and bone-marrow depression are the most life-threatening. Hypotension and interference with temperature regulation are dose-related. They can result in dangerous falls and hypothermia in the elderly and this must be considered before prescribing these drugs for patients over 70 years of age.

Extrapyramidal symptoms are the most troublesome and are caused most frequently by the piperazine phenothiazines such as fluphenazine, the butyrophenones such as haloperidol and the depot preparations. Although easily recognized, they are not so easy to predict because they depend in part on the dose and patient susceptibility as well as the type of drug. However, there is a general tendency for low-potency drugs to have less extrapyramidal adverse effects, while high-potency drugs such as haloperidol have more extrapyramidal effects but less sedation and anticholinergic (more correctly antimuscarinic) effects. Sedation and anticholinergic effects usually diminish with continued use. Extrapyramidal symptoms consist of parkinsonian-type symptoms including tremor which may occur gradually; dystonia (abnormal face and body movements) and dyskinesia, which may appear after only a few doses; akathisia (restlessness), which may occur after large initial doses and may resemble an exacerbation of the condition being treated; and tardive dyskinesia (an orofacial dyskinesia), which usually takes longer to develop but may develop on short-term treatment with low doses; short-lived tardive dyskinesia may occur after withdrawal of the drug. Parkinsonian symptoms are usually reversible on withdrawal of the drug and may be suppressed by anticholinergic (antimuscarinic) drugs but they may unmask or worsen tardive dyskinesia. Tardive dyskinesia is usually associated with long-term treatment and high dosage of an antipsychotic, particularly in elderly patients (see section 9.2). There is no established treatment for tardive dyskinesias, which may be irreversible on withdrawing therapy. However, withdrawal at the earliest signs of tardive dyskinesia may halt its full development. Treatment of all patients on antipsychotics must be carefully and regularly reviewed.

Neuroleptic malignant syndrome (hypothermia, fluctuating levels of consciousness, muscular rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating and urinary incontinence) is a rare adverse effect of haloperidol and chlorpromazine. It is managed by discontinuing the antipsychotic, correcting fluid and electrolyte defects, and giving bromocriptine and sometimes dantrolene.

CHLORPROMAZINE HYDROCHLORIDE

Chlorpromazine is a representative antipsychotic. Various drugs can serve as alternatives

**WARNING.**
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

**Tablets**, chlorpromazine hydrochloride 50 mg, 100mg

**Injection** (Solution for injection), chlorpromazine hydrochloride 25 mg/ml, 2-ml ampoule

**Uses:**
- schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety

**Contraindications:**
- impaired consciousness due to CNS depression; bone-marrow depression; phaeochromocytoma

**Precautions:**
- cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection; **interactions:** Appendix 1

**Patient advice.**
May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage:**
- Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, and severe anxiety (adjunct), by mouth, **ADULT** initially 25 mg 3 times daily (or 75 mg at night) adjusted according to response to usual maintenance dose of 100–300 mg daily (but up to 1.2 g daily may be required in psychoses); **ELDERLY** (or debilitated) third to half adult dose; **CHILD** (childhood schizophrenia and autism) 1–5 years 500 micrograms/kg every 4–6 hours (maximum 40 mg daily); 6–12 years, third to half adult dose (maximum 75 mg daily)
- For relief of acute symptoms, **ADULT** 25–50 mg every 6–8 hours; **CHILD** 500 micrograms/kg every 6–8 hours (1–5 years, maximum 40 mg daily; 6–12 years, maximum 75 mg daily) (see also Precautions and Adverse effects)

**Adverse effects:**
- extrapyramidal symptoms and on prolonged administration, occasionally potentially irreversible tardive dyskinesias (see Belize Drug Formulary and Therapeutics Manual Ninth Edition 2009-2011
notes above); hypothermia (occasionally pyrexia), drowsiness, apathy, pallor, nightmares, dizziness, excitement, insomnia, headache, confusion, depression; more rarely, agitation, EEG changes, convulsions, nasal congestion; anticholinergic symptoms including dry mouth, constipation, blurred vision, difficulty in micturition; hypotension, tachycardia and arrhythmias; ECG changes; respiratory depression; menstrual disturbances, galactorrhoea, gynaecomastia, impotence, weight gain; sensitivity reactions such as agranulocytosis, leukopenia, leukocytosis, haemolytic anaemia, photosensitization, contact sensitization and rashes, jaundice and alterations in liver function; neuroleptic malignant syndrome; lupus erythematosus-like syndrome; with prolonged high dosage, corneal and lens opacities, and purplish pigmentation of the skin, cornea and retina; intramuscular injection may be painful and cause hypotension and tachycardia (see Precautions) and nodule formation.

**HALOPERIDOL**

Haloperidol is a representative antipsychotic. Various drugs can serve as alternatives.

**Tablets**, haloperidol 5 mg

**Injection** (Solution for injection), haloperidol 5 mg/ml, 1-ml ampoule, 2ml

**Uses:** schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety.

**Contraindications:** impaired consciousness due to CNS depression; bone-marrow depression; phaeochromocytoma; porphyria; basal ganglia disease.

**Precautions:** cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood count required if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcemia, or hypomagnesaemia; elderly (particularly in very hot or very cold weather); children and adolescents; avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection;

**Interactions:** Appendix 1

**Patient advice.** May impair ability to perform skilled tasks, for example operating machinery, driving.

**Dosage:**

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, and severe anxiety (adjunct), by mouth. ADULT initially 1.5–3 mg 2–3 times daily or 3–5 mg 2–3 times daily in severely affected or resistant patients (up to 30 mg daily in resistant schizophrenia); ELDERLY (or debilitated) initially half adult dose; CHILD initially 25–50 micrograms/kg daily in 2 divided doses (maximum 10 mg daily)

Acute psychotic conditions, by intramuscular injection, ADULT initially 2–10 mg, subsequent doses every 4–8 hours according to response (up to every hour if necessary) to total maximum of 18 mg; severely disturbed patients may require initial dose of up to 18 mg; elderly (or debilitated) initially half adult dose; CHILD not recommended

Adverse effects: as for Chlorpromazine Hydrochloride (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; pigmentation and photosensitivity reactions rare; extrapyramidal symptoms are common, particularly acute dystonia and akathisia (especially in thyrotoxic patients); rarely weight loss, hypoglycaemia, inappropriate antidiuretic hormone secretion

FLUPHENAZINE

Fluphenazine is a representative depot antipsychotic, used if compliance unlikely to be reliable. Various drugs can serve as alternatives

Oily injection (Solution for injection), fluphenazine decanoate 25 mg/ml, 10-ml ampoule

Uses: maintenance treatment of schizophrenia and other psychoses

Contraindications: children; confusional states; impaired consciousness due to CNS depression; parkinsonism; intolerance to antipsychotics; depression; bone-marrow depression; phaeochromocytoma

Precautions: treatment requires careful monitoring for optimum effect; initial small test dose as adverse effects are prolonged; extrapyramidal symptoms occur frequently; when transferring from oral to depot therapy, dosage by mouth should be reduced gradually; cardiovascular and cerebrovascular disorders, respiratory disease, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood counts if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; elderly (particularly in very hot or very cold weather); interactions: Appendix 1

Patient advice.

May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:
Maintenance in schizophrenia and other psychoses, *by deep intramuscular injection* into gluteal muscle, **ADULT** test dose of 12.5 mg (6.25 mg in elderly), then after 4–7 days 12.5–100 mg repeated at intervals of 2–5 weeks, adjusted according to response; **CHILD** not recommended

**ADMINISTRATION.**
According to manufacturer’s directions

**Adverse effects:**
as for Chlorpromazine Hydrochloride (see above), but less sedating and fewer hypotensive and anticholinergic symptoms; higher incidence of extrapyramidal symptoms (most likely to occur a few hours after injection and continue for about 2 days but may be delayed); systemic lupus erythematosus; pain at injection site, occasionally erythema, swelling, nodules

**THIORIDAZINE**

Tablet, thioridazine hydrochloride, 25 mg, 100 mg

**Uses:**
under specialist supervision, second-line treatment of schizophrenia in adults

**Contraindications:**
significant cardiac disease, such as angina, bradycardia, second-or-third-degree heart block, cardiac failure, history of ventricular arrhythmia, QT-interval prolongation or a family history of the condition, uncorrected hypokalaemia or hypomagnesaemia

**Cautions:**
ECG screening and electrolyte measurement before treatment, after each dose increase and at 6-month intervals; also monitor for visual defects on prolonged use; avoid in porphyria

**Dosage:**
50-300 mg daily (initially in divided doses); max. 600 mg daily (in hospital patients only), **CHILD** not recommended

**Adverse effects:**
less sedating than chlorpromazine, and extrapyramidal symptoms and hypothermia rarely occur; more likely to induce hypotension and increased risk of cardiotoxicity and prolongation of QT interval, pigmentary retinopathy (with reduced visual acuity, brownish colouring of vision and impaired night vision) occurs rarely with high doses; sexual dysfunction, particularly retrograde ejaculation, may occur

**FLUPENTHIXOL**

Tablet, 1 mg

**Uses:**
Schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity; depression

**Contraindications:**
see under chlorpromazine

**Precautions:**
see under chlorpromazine

**Dosage:**
psychoses, initially 3-9 mg twice daily adjusted according to the response; max 18 mg daily; ELDERLY (or delibitated) initially quarter to half adult dose; CHILD not recommended

Fluphenixol has also been given as the hydrochloride, by mouth, for the treatment of mild to moderate depression. The usual initial dose, expressed in terms of the equivalent amount of fluphenixol, is 1 mg (0.5 mg in the elderly) daily, increased after 1 week to 2 mg (1 mg in the elderly) and then to a maximum of 3 mg (2 mg in the elderly) daily. Doses above 2 mg (1 mg in the elderly) should be given in two divided doses. The last dose of the day should be given no later than 4 p.m. and if no effect has been noticed within 1 week of administration of the maximum dose, the treatment should be withdrawn

**Adverse effects:**
see under chlorpromazine; however less sedating but extrapyramidal symptoms frequent

**TRIFLUPERAZINE**

*Tablet*, trifluperazine (as hydrochloride) 5 mg

**Uses:**
see under dosage

**Contraindications:**
see under chlorpromazine

**Precautions:**
see under chlorpromazine

**Dosage:**
by mouth (reduce initial doses in the elderly by at least half)

Schizophrenia and other psychoses, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, initially 5 mg twice daily, increased by 5 mg after 1 week, then at intervals of 3 days, according to the response; CHILD up to 12 years, initially up to 5 mg daily in the divided doses, adjusted to response, age, and body-weight

Short-term adjunctive management of severe anxiety, 2-4 mg daily in the divided doses or 2-4 mg daily in modified-release form, increased if necessary to 6 mg daily; CHILD 3-5 years up to 1 mg daily, 6-12 years up to 4 mg daily

**Adverse effects:**
see under chlorpromazine; extrapyramidal symptoms more fre-
quent especially at doses exceeding 6 mg daily; pancytopenia; thrombocytopenia; hyperexia; anorexia

**QUETIAPINE**

*Tablet, 50 mg, 200 mg*

**Uses:** schizophrenia, treatment of episodes of mania either alone or with mood stabilizers

**Contraindications:** breast-feeding

**Precautions:** use with care in pregnancy, patients with impaired liver and kidney functions

**Dosage:**
- Schizophrenia: 25 mg twice daily on day 1, 50 mg twice daily on day 2, 100 mg twice daily on day 3, 150 mg twice daily on day 4, then adjusted according to response, usual range 300-450 mg daily in two divided doses; max 750 mg daily; ELDERLY initially 25 mg daily in 2 divided doses, increased in steps of 25-50 mg daily; CHILD and ADOLESCENT not recommended.
- Mania: 50 mg twice daily on day 1, 100 mg twice daily on day 2, 150 mg twice daily on day 3, 200 mg twice daily on day 4, then adjusted according to response in steps of up to 200 mg daily to max. 800 mg daily; usual range 400-800 mg daily in 2 divided doses, increased in steps of 25-50 mg daily; CHILD and ADOLESCENT not recommended.

**Adverse effects:** dizziness, weight gain, postural hypotension, transient antimuscarinic effects; drowsiness, mild asthenia, tachycardia, anxiety, fever, myalgia, ear pain, rash, leucopenia, neutropenia and occasionally eosinophilia reported; elevated plasma-triglyceride and cholesterol concentrations, reduced plasma-thyroid hormone concentrations; possible QT interval prolongation; rarely oedema; very rarely priapism

**RISPERIDONE**

*Tablet, risperidone 2 mg*

*Injection, powder for reconstitution, risperidone 25 mg/vial*

**Uses:** acute and chronic psychoses, mania

**Contraindications:** breast-feeding

**Precautions:** use with care in patients with impaired liver, kidney and cardiovascular functions, paralytic ileus, diabetes mellitus, bone-marrow depression, low leucocyte or neutrophil count, prostatic
hyperplasia, parkinson’s disease

**Dosage:**
psychoses, 2mg in 1-2 divided doses on first day then 4mg in 1-2 divided doses on second day (slower titration appropriate in some patients); usual dose range from 4-6mg daily; doses above 10mg daily only if benefit considered to outweigh risk (max, 16mg daily); Elderly (or in hepatic or renal impairment) initially 500 micrograms twice daily increased in steps of 500micrograms twice daily to 1-2 mg twice daily; Child under 15 years not recommended.

Mania, initially 2mg once daily, increased if necessary in steps of 1mg daily; usual dose range from 1-6mg daily; Elderly (or in hepatic or renal impairment) initially 500micrograms twice daily increased in steps of 500 micrograms twice daily to 1-2mg twice daily.

By deep intramuscular injection into the gluteal muscle, patients taking oral risperidone up to 4 mg daily, initially 25 mg every 2 weeks; patients taking oral risperidone over 4 mg daily, initially 37.5 mg every 2 weeks; dose adjusted at intervals of at least 4 weeks in steps of 12.5 mg to max. 50 mg(ELDERLY 25 mg) every 2 weeks; CHILD and ADOLESCENTS under 18 years not recommended.

**Adverse effects:**
anxiety, agitation, insomnia, headache, drowsiness, impaired concentration,blurred vision, fatigue, constipation, nausea,vomiting, abdominal pain,hyperprolactinaemia,sexual dysfunction,priapism, urinary incontinence, tarchycardia, rash

**CLOZAPINE**

*Tablet,* 25 mg, 50 mg, 100 mg

**Uses:**
schizophrenia (including psychosis in Parkinson’s disease) in patients unresponsive to, or intolerant of conventional antipsychotic drugs

**Contra-indications:**
severe cardiac disorders (e.g. myocarditis), active liver disease, severe renal impairment; history of neutropenia or agranulocytosis; bone-marrow disorders; paralytic ileus; alcoholic and toxic psychoses; history of circulatory collapse; coma or severe CNS depression; uncontrolled epilepsy; pregnancy and breast-feeding

**Cautions:**
monitor leucocyte and differential blood counts; taper off conventional neuroleptic before starting; hepatic impairment; renal impairment; prostatic hypertrophy, angle- closure glaucoma

**WITHDRAWAL.** On planned withdrawal reduce dose over 1-2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary, observe patient carefully.
AGRANULOCYTOSIS. Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor count every week for 18 weeks then at least every 2 weeks and if clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm³ or if absolute neutrophil count below 1500/mm³ discontinue permanently and refer to haematologist. Avoid drugs which depress leucopoiesis; patients should report immediately symptoms of infection especially influenza-like illness.

MYOCARDITIS AND CARDIOMYOPATHY. Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported. It is advised that

- physical examination and medical history before starting clozapine
- specialist examination if cardiac abnormalities or history of heart disease found-clozapine initiated only in absence of severe heart disease and if benefit outweighs risk
- persistent tachycardia especially in the first 2 months should prompt observation for other indications for myocarditis or cardiomyopathy
- if myocarditis or cardiomyopathy suspected clozapine should be stopped and patient evaluated urgently by cardiologist
- discontinue permanently in clozapine induced myocarditis or cardiomyopathy

GASTRO-INTESTINAL OBSTRUCTION. Reactions resembling gastro-intestinal obstruction reported. Clozapine should be used cautiously with drugs which cause constipation (antimuscarinic drugs) or in history of colonic disease or bowel surgery. Monitor for constipation and prescribe laxative if required

Dosage:
schizophrenia, ADULT over 16 years (close medical supervision on initiation- risk of collapse due to hypotension) 12.5 mg once or twice on the first day then 25-50 mg on the second day then increased gradually (if well tolerated) in steps of 25-50 mg daily over 14-21 days up to 300 mg daily in divided doses (larger dose at night, up to 200 mg daily may be taken as a single dose at bedtime); if necessary may be further increased in steps of 50-100 mg once (preferably) or twice weekly; usual dose 200-450 mg daily (max. 900 mg)

NOTE. Restarting after interval of more than 2 days, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation – extreme caution if previous or cardiac arrest with initial dosing

ELDERLY AND SPECIAL INTEREST GROUPS. In elderly,
12.5 mg once first day – subsequent adjustments restricted to 25 mg daily

Psychosis in Parkinson’s disease, ADULT over 16 years, 12.5 mg at bedtime then increased in steps of 12.5 mg up to twice weekly to 50 mg at bedtime; usual dose range of 25-37.5 mg at bedtime; exceptionally, dose may be increased further in steps of 12.5 mg weekly to max. 100 mg daily in 1-2 divided doses

**Adverse effects:**

see notes above; also constipation, hypersalivation, nausea, vomiting, tachycardia, ECG changes, hypertension, drowsiness, blurred vision, headache, tremor, rigidity, extrapyramidal symptoms, convulsions, fatigue, impaired temperature regulation, fever, hepatitis, cholestatic jaundice, pancreatitis, urinary incontinence and retention

**Drugs used in mood disorders**

Mood disorders can be classified as depression (unipolar disorder) and mania; alternating episodes of mania and depression (manic depression) are termed bipolar disorder. Electroconvulsive therapy (ECT) has been shown to be rapidly effective in the urgent treatment of severe depression. Counselling and psychotherapy have an important role in treating some forms of depression.

**Drugs used in depressive disorders**

Tricyclic and related antidepressants and the more recently introduced selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs in the treatment of depressive disorders. The response to antidepressant therapy is usually delayed with a lag-period of up to two weeks and at least six weeks before maximum improvement occurs. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. The use of more than one antidepressant at a time is not recommended since this does not enhance effectiveness and it may result in enhanced adverse effects or interactions.

Patients should be reviewed every 1–2 weeks at the start of treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to change to another antidepressant due to lack of efficacy. In the case of a partial response, treatment may be continued for a further 2 weeks (elderly patients may take longer to respond). Remission usually occurs after 3–12 months. Treatment at full therapeutic dose should be continued for at least 4–6 months after resolution of symptoms (about 12 months in the elderly). Treatment should not be withdrawn prematurely otherwise symptoms are likely to recur. Patients with a history of recurrent depression should continue to receive maintenance treatment (for at least 10/16/2008 9:54:03 AM

5 years and possibly indefinitely). Lithium may be used as an alternative for maintenance treatment (see section 24.2.2). Reduction in dose should be gradually carried out over a period of about 4 weeks or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

Tricyclic and related antidepressants can be divided into those with more or less sedative effect. Those with sedative properties include amitriptyline and those with less sedative effects include imipramine. These drugs are most effective in the treatment of depression associated with psychomotor and physiological disturbances. Adverse effects include anticholinergic (more correctly antimuscarinic) symptoms of dry mouth, blurred vision, constipation and urinary retention. Arrhythmias and heart block can occur. Minimal quantities of tricyclic antidepressants should be prescribed at any one time because they are dangerous in overdose.

The SSRIs characteristically cause gastrointestinal disturbances, sleep disturbances and hypersensitivity reactions including rash (may be a sign of an impending serious systemic reaction and discontinuation should be considered) but they are less sedating and have fewer anticholinergic (antimuscarinic) and cardiotoxic effects than tricyclic antidepressants. The SSRIs are less toxic in overdose than the older tricyclic compounds. They may be preferred in patients in whom the risk of suicide is strong, but there is some concern that SSRIs may increase suicidal ideation.

**AMITRIPTYLINE HYDROCHLORIDE**

Amitriptyline hydrochloride is a representative tricyclic antidepressant. Various drugs can serve as alternatives

**Tablets**, amitriptyline hydrochloride 25 mg, 75 mg

**Uses:**
Moderate to severe depression

**Contraindications:**
Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria

**Precautions:**
cardiac disease (see Contraindications above), history of epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; hepatic impairment (Appendix 5); thyroid disease; phaeochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); **interactions:** Appendix 1

**Patient Advice.**

May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage:**
Depression, *by mouth*, **ADULT** initially 75 mg (elderly and adolescents 30–75 mg) daily in divided doses or as a single dose at bedtime increased gradually as necessary to 150–200 mg daily; **CHILD** under 16 years not recommended for depression

**Adverse effects:**
- sedation, dry mouth, blurred vision (disturbance of accommodation, increased intra-ocular 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); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), 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; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test
- In overdose, excitement, restlessness, marked anticholinergic effects; severe symptoms including unconsciousness, convulsions, myoclonus, hyperreflexia, hypotension, acidosis, respiratory and cardiac depression with arrhythmias

**IMIPRAMINE**

*Tablet*, imipramine hydrochloride 25 mg

**Uses:** depressive, illness, panic disorders, treatment of juvenile enuresis.

**Contraindications:** patients on MAO inhibitors or Fluoxetine within 14 days; narrow angle glaucoma

**Precautions:** see under amitriptyline

**Dosage:** depression, initially up to 75 mg daily in divided doses, increased gradually to 150-200 mg (up to 300 mg in hospital patients); up to 150 mg may be given as a single dose at bedtime; **ELDERLY** initially 10 mg daily, increased gradually to 30-50 mg daily; **CHILD** not recommended for depression.

Niorurnal enuresis, **CHILD** 7 years 25 mg, 8-11 years 25-50 mg, over 11 years 50-75 mg at bed-time, max. period of treatment (including gradually withdrawal) 3 months-full physical examination before further course

**Adverse effects:** see under amitriptyline, but less sedating

**SERTRALINE**

Tablet, sertraline (as hydrochloride) 50 mg

**Uses:**
Depressive illness, obsessive-compulsive disorder (under specialist supervision in children), post traumatic stress disorder in women

**Contraindications:** patients in maniac phase

**Precautions:**
Use with care in patients with impaired hepatic or renal function, patients with epilepsy or history of such disorders, those with cardiac disease or history of bleeding disorders, early pregnancy (patients should be closely monitored) and breastfeeding, diabetes mellitus,

**Dosage:**
- Depressive illness, initially 50mg daily, increased if necessary by increments of 50mg over several weeks to max. 200mg daily; usual maintenance dose 50mg daily: Child and Adolescent under 18 years not recommended
- Obsessive-compulsive disorder, Adult and Adolescents over 13 years initially 50mg daily, increased if necessary in steps of 50mg over several weeks, usual dose range 50-200mg daily: Child 6-12 years 25mg daily, increased to 50mg daily after 1 week, further increased if necessary in steps of 50mg at intervals of at least 1 week (max. 200mg daily); Child under 6 years not recommended.
- Post-traumatic stress disorder, initially 25mg daily, increased after 1 week to 50mg daily; if response is partial and if drug tolerated dose increased in steps of 50mg over several weeks to max. 200mg daily; Child not recommended

**Adverse effects:** include gastro-intestinal effects (dose-related and common ones are nausea, vomiting, dyspepsia, abdominal pain, diarrhea, constipation), anorexia with weight loss, hypersensitivity reactions including rash, anxiety, restlessness, nervousness, insomnia, drowsiness and fatigue, headache, tremor, dizziness, hallucinations, convulsions. Sertraline (and other selective serotonin re-uptake inhibitors-SSRIs) are less sedating and have fewer antimuscarinic and cardiotoxic effects than tricyclic antidepressants.

**FLUOXETINE**

Tablet, fluoxetine (as hydrochloride) 20 mg

**Uses:**
Depressive illness, bulimia nervosa, obsessive-compulsive disorder

**Contraindications:**
as under sertraline

**Precautions:**
see under sertraline

**Dosage:**
Depressive illness, 20 mg once daily increased after 3 weeks if necessary, usual dose 20-60 mg (ELDERLY 20-40 mg) once daily; max. 80 mg (ELDERLY max. 60 mg) once daily; CHILD and ADOLESCENT under 18 years not recommended

Bulimia nervosa, 60 mg once daily; max. 80 mg daily; CHILD and ADOLESCENT under 18 years not recommended

Obsessive–compulsive disorder, initially 20 mg once daily increased after two weeks if necessary, usual dose 20-60 mg (ELDERLY 20-40 mg) once daily; max. 80 mg (ELDERLY max. 60 mg) once daily; discontinue if no improvement within 10 weeks; CHILD and ADOLESCENT under 18 years not recommended

Adverse effects: possible changes in blood sugar, fever, neuroleptic malignant syndrome-like event; also reported (no causal relationship established); abnormal bleeding, aplastic anaemia, cerebrovascular accident, gastro-intestinal haemorrhage, haemolytic anaemia, pancytopenia, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding on withdrawal, violent behaviour; hair loss also reported

Drugs used in bipolar disorders

Treatment of bipolar disorders has to take account of three stages: treatment of the acute episode, continuation phase and prophylaxis to prevent further episodes. Lithium is effective in acute mania but symptomatic control of the florid symptoms with an antipsychotic or benzodiazepine is often necessary whilst waiting for the antimania drug to exert its effect. Benzodiazepines may be given during the initial stages until lithium becomes effective but they should not be used for long periods because of the risk of dependence. Lithium may be given concurrently with antipsychotics and treatment with the antipsychotic should be tailed off as lithium becomes effective. Alternatively, lithium therapy may be delayed until the patient’s mood is stabilized with the antipsychotic. However, there is a risk of neurotoxicity and increased extrapyramidal disorders when lithium and antipsychotics are used concurrently (Appendix 1). Lithium is the mainstay of treatment but its narrow therapeutic range is a disadvantage. Sodium valproate is effective and carbamazepine may also be used. Treatment of depressive episodes in bipolar disorders will mostly involve combination treatment using either lithium or sodium valproate together with a tricyclic antidepressant. Increased adverse effects are a problem which may compromise treatment. Lithium prophylaxis should usually only be undertaken with specialist advice and the likelihood of recurrence considered. Long-term lithium therapy has been associated with thyroid disorders and mild cognitive and memory impairment. Patients should continue the treatment for longer than 3 to 5 years only.
Withdrawal appears to produce high levels of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a few weeks and patients should be warned of possible relapses if discontinued abruptly. Lithium salts have a narrow therapeutic/toxic ratio and should only be prescribed if there are facilities for monitoring serum lithium concentrations. Doses are adjusted to achieve serum-lithium concentrations of 0.4–1 mmol/litre (lower end of range for maintenance therapy and the elderly) on samples taken 12 hours after the preceding dose. The optimum range for each patient should be determined.

Overdosage, usually with serum-lithium concentration of over 1.5 mmol/litre may be fatal and toxic effects include coarse tremor, ataxia, dysarthria, nystagmus, renal impairment and convulsions. If any of these effects occur, treatment should be stopped, serum-lithium concentration determined and in mild overdosage large amounts of sodium and fluid should be given to reverse the toxicity; in severe toxicity, haemodialysis may be required.

For patients who are unresponsive to or intolerant of lithium, carbamazepine may be used in the prophylaxis of bipolar illness particularly in those with rapid cycling affective disorders (more than four affective episodes per year).

**LITHIUM CARBONATE**

*Tablets, capsules,* lithium carbonate 300 mg

**Uses:**
Treatment and prophylaxis of mania, prophylaxis of bipolar disorder and recurrent depression

**Contraindications:**
Renal impairment (Appendix 4); cardiac insufficiency; conditions with sodium imbalance such as Addison disease

**Precautions:**
measure serum-lithium concentration about 4 days after starting treatment, then weekly until stabilized, then at least every 3 months; monitor thyroid function every 6–12 months on stabilized regimens—risk of hypothyroidism (see below); monitor renal function; maintain adequate fluid and sodium intake; reduce dose or discontinue in diarrhoea, vomiting and intercurrent infection (especially if associated with profuse sweating); pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly (reduce dose); diuretic treatment, myasthenia gravis; surgery; if possible, avoid abrupt withdrawal (see notes above); interactions: Appendix 1

**Patient Advice.**
Patients should maintain adequate fluid intake and should
avoid dietary changes which may reduce or increase sodium intake. Patients should be advised to seek medical attention if symptoms of hypothyroidism (for example, feeling cold, lethargy) develop (women are at greater risk)

**NOTE.**

Different preparations vary widely in bioavailability; a change in the preparation used requires the same precautions as initiation of treatment

**Dosage:**

Treatment of mania (general guidelines only, see also note below) *by mouth*, **ADULT** initially 0.6–1.8 g daily (elderly 300–900 mg daily)

Prophylaxis of mania, bipolar disorder and recurrent depression (general guidelines only, see also note below), *by mouth*, **ADULT** initially 0.6–1.2 g daily (elderly 300–900 mg daily)

**NOTE.**

Dosage of lithium depends on the preparation chosen since different preparations vary widely in bioavailability. Dosage should be adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre (lower end of range for maintenance therapy and in elderly) on samples taken 12 hours after a dose and 4–7 days after starting treatment then every week until dosage has remained unchanged for 4 weeks, then every 3 months thereafter

**DOSAGE REGIMENS.**

For dose information for a specific preparation, consult manufacturer's literature

**Adverse effects:**

gastrointestinal disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, weight gain and oedema (may respond to dose reduction); hyperparathyroidism and hypercalcaemia reported; signs of intoxication include blurred vision, muscle weakness, increasing gastrointestinal disturbances (anorexia, vomiting, diarrhoea), increased CNS disturbances (mild drowsiness and sluggishness, increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, dysarthria) and require withdrawal of treatment; with severe overdosage (serum concentrations above 2 mmol/litre), hyperreflexia and hyperextension of the limbs, convulsions, toxic psychoses, syncope, renal failure, circulatory failure, coma, occasionally death; goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, exacerbation of psoriasis and kidney changes may occur

**CARBAMAZEPINE**
Tablets, carbamazepine 200 mg

Uses:
Prophylaxis of bipolar disorder unresponsive to or intolerant of lithium; epilepsy, trigeminal neuralgia (section 5.1)

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

Precautions:
hepatic impairment (Appendix 5); renal impairment (Appendix 4); cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; pregnancy (Appendix 2 (neural tube screening)); breastfeeding (Appendix 3); avoid sudden withdrawal; interactions: Appendix 1

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

Patient Advice.
May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:
Prophylaxis of bipolar disorder, by mouth , ADULT initially 400 mg daily in divided doses increased until symptoms are controlled to a maximum of 1.6 g daily; usual maintenance range 400–600 mg daily

Adverse effects:
dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma concentrations); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and
agitation in elderly

**SODIUM VALPROATE**

*Enteric-coated tablets* (Gastro-resistant tablets), sodium valproate 200mg or 250 mg, 500mg

**Uses:**
Acute mania; epilepsy (section 5.1)

**Contraindications:**
Active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria

**Precautions:**
monitor liver function before and during therapy (Appendix 5), especially in patients at most risk (those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation); ensure no undue potential for bleeding before starting and before major surgery or anticoagulant therapy; renal impairment (Appendix 4); pregnancy (Appendix 2 (neural tube screening)); breastfeeding (Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; interactions: Appendix 1

**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 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

**Dosage:**
Acute mania, *by mouth*, ADULT initially 750 mg daily in divided doses, increased as quickly as possible to achieve the optimal response (maximum 60 mg/kg daily)

**Adverse effects:**
gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (see Precautions—withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness); sedation reported and also increased alertness; behavioural disturbances; rarely pancreatitis (measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss,
Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism, and acne reported

**Drugs used in anxiety and sleep disorders**

The most widely used anxiolytics and hypnotics are the benzodiazepines. Treatment of anxiety should be limited to the lowest effective dose for the shortest possible time. The cause of insomnia should be established and appropriate treatment for underlying factors instituted before hypnotics are considered. Hypnotics may be of value for a few days but rarely longer than a week.

Tolerance and dependence (both physical and psychological) and subsequent difficulty in withdrawing the drug may occur after regular use for more than a few weeks. Patients with chronic anxiety, alcohol or drug dependence or those with personality disorders are more likely to become dependent. Anxiolytics and hypnotics should be prescribed in carefully individualized dosage and use should be limited to control of acute conditions such as panic attacks and acute anxiety and severe, incapacitating insomnia. There is usually no justification for prolonging treatment with anxiolytics and hypnotics for more than one to two weeks.

If used for longer periods, withdrawal should be gradual by reduction of the dose over a period of weeks or months, as abrupt discontinuation may produce confusion, toxic psychosis, convulsions or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine but may occur within a few hours in the case of a short-acting one. The syndrome is characterized by insomnia, anxiety, loss of appetite and body-weight, tremor, perspiration, tinnitus and perceptual disturbances. These symptoms may be similar to the original complaint and encourage further prescribing. Some symptoms may continue for weeks or months after stopping benzodiazepines.

Patients should be warned that their ability to drive or operate machinery may be impaired and that the effects of alcohol may be enhanced.

**DIAZEPAM**

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

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

*Tablets*, diazepam 5 mg
*Injection*, diazepam 5mg/ml

24.1 Drugs used in psychotic disorders

Uses:
Short-term treatment of anxiety and insomnia; status epilepticus, recurrent seizures; febrile convulsions, adjunct in acute alcohol withdrawal (section 5.1); premedication (section 1.3)

Contraindications:
Respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis

Precautions:
respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (Appendix 2); breastfeeding (Appendix 3); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 5), renal impairment (Appendix 4); avoid prolonged use and abrupt withdrawal; porphyria; interactions: Appendix 1

Patient Advice
May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:
Anxiety, by mouth , ADULT 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; ELDERLY (or debilitated) half adult dose
Insomnia, by mouth , ADULT 5–15 mg at bedtime

Adverse effects:
drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice; skin reactions; raised liver enzymes

LORAZEPAM

Tablet, lorazepam 1 mg
Injection, lorazepam 4 mg/ml

Uses:
Anxiety, insomnia, especially useful for the elderly.

Contraindications:
see under diazepam

Precautions: see under diazepam

Dosage: By mouth, anxiety, 1-4 mg daily in divided doses; Elderly (debilitated) half adult dose
Insomnia associated with anxiety, 1-2 mg at bed-time; Child not recommended
By intramuscular or slow intravenous injection (into a large vein), acute panic attacks, 25-30 micrograms/kg (usual range 1.5-2.5 mg), repeated every 6 hours if necessary, CHILD not recommended.

NOTE
Only use intramuscular route when oral and intravenous routes are not possible. **Adverse effects:** see under diazepam

**ALPRAZOLAM**
*Tablet, 0.25 mg*

**Uses:**  
Anxiety (short-term use)  
Contraindications:  
see under diazepam  
**Precautions:**  
see under diazepam  
**Dosage:**  
**ADULTS:** 0.25-0.5 mg 3 times daily (elderly or delibitated 0.25 mg 2-3 times daily), increased if necessary to 3 mg daily. **CHILD** not recommended.  
**Adverse effects:** see under diazepam

**CLONAZEPAM**
*Tablet, clonazepam 1 mg*

**Uses:** see under the section on anticonvulsants

**DIPHENHYDRAMINE**

*Tablet, 25 mg, 50 mg Injection, 25 mg, 50 mg*

**Uses:**  
Symptomatic relief of allergic symptoms, mild nighttime sedation, prevention of motion sickness and as an antitussive, treatment of antipsychotic-induced extrapyramidal symptoms.  
**Contraindications:**  
Hypersensitivity to diphenhydramine or any component of its formulation; acute asthma; not for use in neonates  
**Precautions:**  
Causes sedation, caution must be used in performing tasks which require alertness; sedative effects of CNS depressants or alcohol are potentiated. Diphenhydramine has high sedative and anticholinergic properties, so it may not be considered the antihistamine of choice for prolonged use in the elderly.  
**Dosage:**  
**CHILDREN; treatment of moderate to severe reactions:** 5 mg/kg/day or 150 mg/m2/day in divided doses every 6-8 hours, not to exceed 300 mg/day Minor allergic rhinitis or motion sickness; 2 to less than 6 years, 6.25 mg every 4 hours. max. 37.5 mg/day; 6- less than 12 years, 12.5-25 mg every 4-6 hours, max. 150 mg/day; above 12 years; 25-50 mg every 4-6 hours, max. 300 mg/day Night-time sleep aid: 30 minutes before bedtime; 2 to less than12 years 1 mg/kg/dose: max. 50mg/dose; above
24.1 Drugs used in psychotic disorders

12 years, 50 mg/dose Antitussive: 2 to less than 6 years, 6.25 mg every 4 hours. max. 37.5 mg/day; 6- less than 12 years, 12.5 mg every 4-6 hours, max. 75 mg/day; above 12 years; 25 mg every 4-6 hours, max. 150 mg/day ADULTS; oral: 25-50 mg every 6-8 hours Minor allergic rhinitis or motion sickness: 25-50 mg every 4 -6 hours; max.300 mg/day Moderate to severe allergic reactions: 25-50 mg every 4 hours, not to exceed 400 mg/ day Nighttime sleep aid: 50 mg at bedtime

**Adverse effects:**
Nausea, vomiting, sedation, dry mucous membrane, urinary retension, sedation, dizziness

**Obsessive-compulsive disorders and panic attacks**

Obsessive-compulsive disorders can be treated with a combination of pharmacological, behavioural and psychological treatments. Antidepressants such as clomipramine which inhibit reuptake of serotonin have been found to be effective. Panic attacks may be treated with behavioural or cognitive therapy. If this management fails, drug therapy may be tried. Some tricyclic antidepressants including clomipramine, or SSRIs can reduce frequency of attacks or prevent them completely. Benzodiazepines may be used in panic attacks resistant to antidepressants.

**CLOMIPRAMINE HYDROCHLORIDE**

Capsules, clomipramine hydrochloride 10 mg, 25 mg

**Uses:**
Phobic and obsessional states; panic attacks

**Contraindications:**
Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria

**Precautions:**
cardiac disease (see Contraindications above), history of epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3); elderly; hepatic impairment (Appendix 5); thyroid disease; phaeochromocytoma; history of mania, psychoses (may aggravate psychotic symptoms); angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); **interactions:** Appendix 1

**Patient Advice**
May impair ability to perform skilled tasks, for example operating machinery, driving

**Dosage:**
Phobic and obsessional states, **by mouth**. ADULT initially 25 mg daily, usually at bedtime (ELDERLY 10 mg daily) increased
over 2 weeks to 100–150 mg daily; **CHILD** not usually recommended

**Adverse effects:**
- sedation, dry mouth, blurred vision (disturbance of accommodation, increased intra-ocular 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); behavioural disturbances; hypomania or mania, confusion (particularly in elderly), 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; convulsions, movement disorders and dyskinesias, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test
- Methylphenidate (Ritalin)

*Tablet,* 10 mg, 20 mg sustained release

**Uses:**
- Part of a comprehensive treatment programme for attention-deficit hyperactivity disorder when remedial measures alone prove insufficient (under specialist supervision)

**Contraindications:**
- Cardiovascular disease including moderate to severe hypertension, hyperexcitability or agitated states, hyperthyroidism, history of drug or alcohol abuse, glaucoma, pregnancy and breast-feeding

**Precautions:**
- Mild hypertension- monitor blood pressure; history of epilepsy (discontinue if convulsions occur); tics and Tourette syndrome (use with caution)-discontinue if tics occur: monitor growth in children; avoid abrupt withdrawal: data on safety and efficacy of long term use not complete, porphyria; manufacturer recommends periodic complete and differential blood and platelet counts

**Dosage:**
- **CHILD** over 6 years, initially 5 mg 1-2 times daily, increased if necessary at weekly intervals by 5-10 mg daily to max. 60 mg daily in divided doses; discontinue if there is no response after 1 month, also suspend periodically to assess child’s condition (usually finally discontinued during or after puberty; under 6 years not recommended

**EVENING DOSE,** if effect wears off in evening (with rebound hyperactivity), a dose at bedtime may be appropriate (establish need with bedtime trial dose)

**Adverse effects:**
- insomnia, restlessness, irritability and excitability, nervousness,
night terrors, euphoria, tremor, dizziness, headache, convulsions, dependence, tolerance, sometimes psychoses; anorexia, gastrointestinal symptoms, growth retardation in children, dry mouth, sweating, tachycardia, palpitations, increased blood pressure, visual disturbances, sleep disturbances, depression, confusion
24.1 Drugs used in psychotic disorders
SECTION 25:
DRUGS ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic drugs
Drugs acting on the respiratory tract

25.1 Antiasthmatic drugs

Asthma

Asthma is a chronic inflammatory disease characterized by episodes of reversible airways obstruction due to bronchial hyperresponsiveness; inflammation may lead to irreversible obstruction in a few patients. A classification based on severity before the start of treatment and disease progression is of importance when decisions have to be made about management. It can be divided by severity into intermittent, mild persistent, moderate persistent and severe persistent. These are useful in the management of the disease since therapy has a stepwise approach which must be discussed with the patient before commencing therapy. The level of therapy is increased as the severity of the asthma increases with stepping-down if control is sustained (see tables on treatment below).

INHALATION

Medications for asthma can be administered in several different ways, including inhaled, oral and parenteral (subcutaneous, intramuscular, or intravenous). The main advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively and rapidly to the airways, and systemic adverse effects avoided or minimized.

It is important that patients receive careful instruction in the use of pressurized (aerosol) inhalation (using a metered-dose inhaler) to obtain optimum results. Before use, the inhaler should be shaken well. After exhaling as completely as possible, the mouthpiece of the inhaler should be placed well into the mouth and the lips firmly closed around it. The patient should inhale deeply through the mouth while actuating the inhaler. After holding the breath for 10 seconds or as long as is comfortable, the mouthpiece should be removed and the patient should exhale slowly.

It is important to check that patients continue to use their inhalers correctly as inadequate technique may be mistaken for drug failure. Spacing devices provide a space between the inhaler and the mouth. They may be of benefit for patients such as the elderly, small children and the asthmatic who find inhalers difficult to use or for those who have difficulty synchronizing their breathing with administration of the aerosol. A large volume spacing device is also recommended for inhalation of high doses of corticosteroids to reduce oropharyngeal deposition which can cause candidosis. The use of metered-dose inhal-
ers with spacers is less expensive and may be as effective as use of nebulizers, although drug delivery may be affected by choice of spacing device. Breath-actuated devices including dry powder inhalers are also available. Solutions for nebulization are available for use in acute severe asthma. They are administered over a period of 5–10 minutes from a nebulizer, usually driven by oxygen in hospital.

**ORAL**
The oral route is used when administration by inhalation is not possible. Systemic adverse effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta$_2$-agonists, corticosteroids, and theophylline.

**PARENTERAL**
Drugs such as beta$_2$-agonists, corticosteroids, and aminophylline may be given by injection in acute severe asthma when administration by nebulization is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

**PREGNANCY**
Poorly controlled asthma in pregnant women can have an adverse effect on the fetus, resulting in perinatal mortality, increased prematurity and low birth-weight. For this reason using medications to obtain optimal control of asthma is justified. Administration of drugs by inhalation during pregnancy has the advantage that plasma drug concentrations are not likely to be high enough to have an effect on the fetus. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia.

**Acute exacerbation 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.

Severe asthma is characterized by persistent dyspnoea poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually more than 110/minute) and a very low peak expiratory flow.

As asthma becomes more severe, wheezing may be absent. Patients should be given oxygen 40–60% (if available) (see also section 1.1.3). Patients should also be given salbutamol or terbutaline via a nebulizer. In emergencies where a nebulizer is not available, salbutamol 100 micrograms by aerosol inhalation can be repeated 10–20 times preferably using a large-volume spacing device. Patients should also be given a corticosteroid; for adults, prednisolone 30–60 mg by mouth or hydrocortisone 200 mg (preferably as sodium succinate).
intravenously; for children, prednisolone 1–2 mg/kg by mouth (1–4 years, maximum 20 mg, 5–15 years, maximum 40 mg) or hydrocortisone 100 mg (preferably as sodium succinate) intravenously; if the patient experiences vomiting the parenteral route may be preferred for the first dose.

If response is inadequate, ipratropium by nebulizer should be considered. Most patients do not benefit from the addition of intravenous aminophylline or a parenteral beta₂-agonist; both cause more adverse effects than nebulized beta₂-agonists. Nevertheless, an occasional patient who has not been taking theophylline, may benefit from a slow intravenous infusion of aminophylline.

The use of epinephrine (adrenaline) (see section 3.1) in asthma has generally been superseded by beta₂-selective adrenoceptor agonists.

Treatment should never be delayed for investigations, patients should never be sedated and the possibility of pneumothorax should be considered. Patients who deteriorate further despite treatment may need intermittent positive pressure ventilation.

TREATMENT OF CHRONIC ASTHMA: INFANTS AND YOUNG CHILDREN UNDER 5 YEARS OLD

Preferred treatments are in bold print

STEP 4

Severe

Long-term Preventive

Daily medications

Quick Relief

• Inhaled short-acting bronchodilator:

Persistent

Long-term Preventive

• Inhaled corticosteroid, beclometasone dipropionate MDI with spacer and face mask > 1 mg daily or nebulized beclometasone > 1 mg twice daily Consider short course of soluble prednisolone tablets, regular inhaled long-acting beta₂-agonist or modified-release theophylline Also, nebulized beta₂–agonist

Quick Relief

bronchodilator: inhaled beta₂-agonist or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily

STEP 3

Moderate

**Long-term Preventive**
Daily medications

**Quick Relief**
- Inhaled short-acting bronchodilator:

**Persistent**

**Long-term Preventive**
- **Inhaled corticosteroid**, beclometasone dipropionate MDI with spacer and face mask 400–800 micrograms daily or nebulized beclometasone <= 1 mg twice daily-
- Consider short course of soluble prednisolone tablets, regular inhaled long-acting beta2-agonist or modified-release theophylline

**Quick Relief**
- **inhaled beta2-agonist** or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily

STEP 2

**Mild**

**Long-term Preventive**
Daily medications

**Quick Relief**
- Inhaled short-acting bronchodilator:

**Persistent**

**Long-term Preventive**
- Either **inhaled corticosteroid**, beclometasone dipropionate, 400–800 micrograms, or cromoglicate (use MDI with a spacer and face mask or use a nebulizer)

**Quick Relief**
- **inhaled beta2-agonist** or ipratropium bromide as needed for symptoms, not to exceed 3–4 times daily

STEP 1

**Intermittent**

**Long-term Preventive**
- None needed

**Quick Relief**
- Inhaled short-acting bronchodilator: **inhaled beta2-agonist** or ipratropium bromide as needed for symptoms, but not more than once daily
- Intensity of treatment will depend on severity of attack

**Step down**
Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.

**Step up**
If control is not achieved, consider step up. But first:
review patient medication technique, compliance and environmental control.

TREATMENT OF CHRONIC ASTHMA:
ADULTS AND CHILDREN OVER 5 YEARS OLD
Preferred treatments are in bold print

STEP 4
Severe
Long-term Preventive
Daily medications
Quick Relief
• Short-acting bronchodilator:

Persistent
Long-term Preventive
Inhaled corticosteroid, beclometasone dipropionate 0.8–2 mg + • Long-acting bronchodilator: either long-acting inhaled beta2-agonist, and/or modified-release theophylline, and/or long-acting beta2-agonist tablets or syrup + • corticosteroid tablets or syrup long term
Quick Relief
inhaled beta2-agonist as needed for symptoms

STEP 3
Moderate
Long-term Preventive
Daily medications
Quick Relief
• Short-acting bronchodilator:

Persistent
Long-term Preventive
Inhaled corticosteroid, beclometasone dipropionate 0.8–2 mg daily in divided doses + if needed • Long-acting bronchodilator: either long-acting inhaled beta2-agonist, modified-release theophylline, or long-acting beta2-agonist tablets or syrup
Quick Relief
• Short-acting bronchodilator: inhaled beta2-agonist as needed for symptoms, not to exceed 3–4 times daily

STEP 2
Mild
Long-term Preventive
Daily medications
Quick Relief
Short-acting bronchodilator:

Persistent

25.1 Antiasthmatic drugs

Long-term Preventive
Either inhaled corticosteroid, beclometasone dipropionate 100–400 micrograms twice daily, sodium cromoglicate or modified-release theophylline

Quick Relief
inhaled beta2-agonist as needed for symptoms, not to exceed 3–4 times daily

STEP 1
Intermittent
Long-term Preventive
• None needed

Quick Relief
• Short-acting bronchodilator: inhaled beta2-agonist as needed for symptoms (up to once daily) • Intensity of treatment will depend on severity of attack • Inhaled beta2-agonist or sodium cromoglicate before exercise or exposure to allergen

Step down
Step down Review treatment every 3 to 6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible.

Step up
If control is not achieved, consider step up. But first: review patient medication technique, compliance and environmental control.

Chronic obstructive pulmonary disease
Chronic obstructive pulmonary disease (chronic bronchitis and emphysema) may be helped by an inhaled short-acting beta2-adrenoceptor agonist used as required or when the airways obstruction is more severe, by an inhaled anticholinergic (antimuscarinic) bronchodilator or both if necessary. Although many patients are treated with an inhaled corticosteroid its role in chronic obstructive pulmonary disease is not clear at present. A limited trial of high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate airflow obstruction to determine the extent of the airway reversibility and to ensure that asthma has not been overlooked. Long-term oxygen therapy prolongs survival in some patients with chronic obstructive pulmonary disease.

Beta2-adrenoceptor agonists (beta2-adrenoceptor stimulants)
The adrenoreceptors in bronchi are mainly beta2 type and their stimulation causes bronchial muscles to relax. The beta2-adrenoceptor agonists include salbutamol, terbutaline, and fenoterol.

When salbutamol is given by inhalation (100–200 micrograms) the effect can last as long as 4 hours thus making it suitable
for both the treatment (see Tables) and prevention of asthma. Salbutamol can also be taken orally in a dose of 2–4 mg up to 4 times daily but is less effective and causes more adverse effects. It can also be given by injection for severe bronchospasm.

**Salmeterol** is a long acting beta 2 agonist which is administered by inhalation. This drug should not be used to relief acute asthma attack

**ADVERSE EFFECTS**
Cardiovascular adverse effects (arrhythmias, palpitations and tachycardia) may occur with salbutamol, but are infrequent with inhaled preparations. Hypokalaemia may result from beta₂-adrenoceptor agonist therapy. Particular caution is required in severe asthma because this effect may be potentiated by concomitant treatment with xanthines (for example theophylline), corticosteroids, diuretics and hypoxia. Plasma potassium concentrations should be monitored in severe asthma.

**Xanthines**

Xanthines include **theophylline** and **aminophylline**. They relax bronchial smooth muscle relieving bronchospasm and also stimulate respiration. Absorption of theophylline from the gastrointestinal tract is usually rapid and complete. It is metabolized by the liver but its half-life can vary considerably in certain diseases including hepatic impairment and cardiac failure, with some coadministered drugs (see Appendix 1) as well as by factors such as age, smoking and alcohol intake. The half-life variation can be important because theophylline has a narrow margin between therapeutic and toxic effects. At therapeutic doses some patients experience nausea and diarrhoea and when plasma concentrations exceed the recommended range of 10–20 mg/litre (55–110 micromol/litre) arrhythmias and convulsions which may be fatal can occur. Monitoring of plasma concentrations is therefore recommended. Theophylline is used to treat chronic asthma, usually in the form of modified-release preparations which produce adequate plasma concentrations for up to 12 hours. It is used as an adjunct to beta₂-agonist or corticosteroid therapy when additional bronchodilation is required but there is an increased risk of adverse effects with beta₂-agonists (see above). When given as a single dose at night, modified-release preparations may be useful in controlling nocturnal asthma and early morning wheezing. The absorption characteristics of modified-release theophylline preparations vary considerably and therefore it is important to keep the patient on the same brand-name formulation.

Theophylline is given by injection as aminophylline (a mixture of theophylline with ethylenediamine) which is 20 times more soluble in water than theophylline alone. It is administered by
slow intravenous injection in severe asthma attacks

**Leukotriene receptor antagonist**

The leukotriene receptor antagonist, *montelukast*, blocks the effects of cysteinyl leukotrienes in the airways. They are effective in asthma when used alone or with inhaled corticosteroids. The leukotriene receptor antagonist maybe of benefit to exercise induce asthma and in those with concomitant rhinitis but they are less effective in severe asthma who are also receiving high dose of other drugs. These drugs should not be used to relieve asthma attack of acute severe asthma.

**Corticosteroids**

**INHALED CORTICOSTEROIDS**

Inhaled corticosteroids, such as *beclometasone*, are the most effective anti-inflammatory medications for the treatment of asthma. They are recommended for the long-term control of asthma in patients using a beta₂-adrenoceptor agonist more than once a day. *Regular use* of inhaled corticosteroids reduces the risk of exacerbations of asthma. Corticosteroids must be used regularly to obtain maximum benefit. Symptom control is usually effective after 3 to 7 days treatment. Long-term high-dose regimens of inhaled corticosteroids are useful for the treatment of severe persistent asthma because they both reduce the need for the long-term use of oral corticosteroids and have fewer systemic adverse effects. Local adverse effects from inhaled corticosteroids include oropharyngeal candidosis, dysphonia and occasional coughing from upper airway irritation. The use of spacing devices reduces oropharyngeal deposition and thus reduces the incidence of candidosis. The risk for systemic effects of inhaled corticosteroids is small and is dependent upon the dose and potency of the corticosteroid as well as its bioavailability and the plasma half-life of its systemically absorbed fraction. Systemic effects are rare and include skin thinning and easy bruising, a small increased risk of glaucoma and cataracts, adrenal suppression, decrease of bone metabolism and growth retardation in children.

**SYSTEMIC CORTICOSTEROIDS**

Oral corticosteroids (sections 3.1 and 18.1) may be used as ‘maximum therapy’ to achieve control of a patient’s asthma. This may be useful either when initiating long-term therapy for a patient with uncontrolled asthma or as a short ‘rescue’ course.
at any stage for acute exacerbation. Long-term oral corticosteroid therapy may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects. In these cases high-dose inhaled corticosteroids should be continued so that oral requirements are reduced to a minimum. Oral doses should be given as a single dose in the morning to reduce the disturbance to the circadian cortisol secretion. Dosage should always be adjusted to the lowest dose which controls symptoms.

Anticholinergic (antimuscarinic) bronchodilators

Ipratropium can provide short-term relief in chronic asthma, but short-acting beta_{2} -agonists work more quickly. Ipratropium is also used as a bronchodilator in chronic obstructive pulmonary disease.

SALBUTAMOL

Salbutamol is a representative beta_{2} -adrenoceptor agonist. Various drugs can serve as alternatives

- **Tablets**, salbutamol (as sulfate), 4 mg
- **Syrup**, salbutamol (as sulfate) 2 mg/5 ml
- **Aerosol inhalation** (Pressurized inhalation), salbutamol (as sulfate) 100 micrograms/metered inhalation
- **Nebulizer solution**, salbutamol (as sulfate) 5 mg/ml, 20-ml ampoules

**Uses:**
- Prophylaxis and treatment of asthma; premature labour (section 22.1)

**Precautions:**
- Hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, pregnancy (but appropriate to use; see also notes above); breastfeeding (Appendix 3); diabetes mellitus—especially intravenous administration (monitor blood glucose; ketoacidosis reported);
- **interactions:** Appendix 1

**Dosage:**
- Chronic asthma (when inhalation is ineffective), **by mouth**, **ADULT** 2–4 mg 3 or 4 times daily; in some patients up to maximum of 8 mg 3 or 4 times daily; **CHILD** under 2 years, 100 micrograms/kg 4 times daily, 2–6 years, 1–2 mg 3–4 times daily, 6–12 years, 2 mg 3–4 times daily
- Severe acute bronchospasm, **by slow intravenous injection**, **ADULT** 250 micrograms, repeated if necessary
- Relief of acute bronchospasm, **by aerosol inhalation**, **ADULT** 100–200 micrograms (1–2 puffs); **CHILD** 100 micrograms (1 puff) increased to 200 micrograms (2 puffs) if necessary; **by intramuscular or subcutaneous injection**, **ADULT** 500 micro-
grams repeated every 4 hours if necessary
Prophylaxis of exercise-induced bronchospasm, by aerosol inhalation, ADULT 200 micrograms (2 puffs); CHILD 100 micrograms (1 puff) increased to 200 micrograms (2 puffs) if required
Chronic asthma (as adjunct in stepped treatment), by aerosol inhalation, ADULT 100–200 micrograms (1–2 puffs) up to 3–4 times daily; CHILD 100 micrograms (1 puff) 3–4 times daily, increased to 200 micrograms (2 puffs) 3–4 times daily if necessary
Severe acute asthma or chronic bronchospasm unresponsive to conventional treatment, by inhalation of nebulized solution, ADULT and CHILD over 18 months, 2.5 mg repeated up to 4 times daily; may be increased to 5 mg if necessary—medical assessment should be considered since alternative therapy may be indicated; CHILD under 18 months, clinical efficacy uncertain (transient hypoxaemia may occur—consider oxygen supplementation)

Adverse effects:
Hypokalaemia after high doses (see notes above); arrhythmias, tachycardia, palpitations, peripheral vasodilation, fine tremor (usually hands), muscle cramps, headache, insomnia, behavioural disturbances in children; hypersensitivity reactions including paradoxical bronchospasm, urticaria and angioedema; slight pain on intramuscular injection

SALMETEROL

Salmetorol is an adrenergic agonist agent; Beta 2- Adrenergic agonist; Bronchodilator
Oral aerosol inhalation, 25mcg/spray (6.5g) (delivers 21mcg/inhalation; 60 inhalation
Use
Maintenance treatment of asthma and in prevention of bronchospasm (inhalation aerosol in patients > 12 years); nocturnal asthma; chronic obstructive airway disease; prevention of exercise induced asthma
Caution:
Precautions: salmeterol is not meant to treat acute asthma attack; acute episodes should be treated with short acting Beta 2 agonist. Do not increase in frequency of salmeterol. All beta agonist may cause increase in heart rate, blood pressure and result in CNS excitement. Use with caution in patients with prostatic hyperplasia, diabetes, cardiovascular disorders, convulsive disorders, thyrotoxicosis. Efficacy under 4 years of age is not established.
Contraindications
Within 2 weeks of MAO Inhibitors
Dosage:
ADULTS: by inhalation: asthma, 50 mcg (2 puffs) or 1 blister) twice a day, up to 100mcg (4 puffs or 2 blisters) twice a day.  
CHILDREN e: 4 years: 50 mcg twice a day.  
Chronic obstructive airway disease: 50 mcg twice a day.  
**Adverse effects:**  
Headache, pharyngitis, palpitations, elevation or depression of blood pressure, tachycardia, insomnia, CNS stimulation, nervousness, GI upset, diarrhea  

**BECLOMETASONE DIPROPIONATE**  
*Aerosol inhalation* (Pressurized inhalation), beclometasone dipropionate 50 micrograms/metered inhalation (standard dose inhaler), 250 micrograms/metered inhalation (high dose inhaler)  
**Uses:**  
Chronic asthma not controlled by short-acting beta _2_ -adrenoceptor agonists  
**Precautions:**  
See notes above; active or quiescent tuberculosis; systemic therapy may be required during periods of stress or when airway obstruction or mucus prevent drug access to smaller airways; not for relief of acute symptoms; monitor height of children receiving prolonged treatment—if growth slowed, review therapy  
**Dosage:**  
Chronic asthma, by *aerosol inhalation* (standard dose inhaler),  
**ADULT** 200 micrograms twice daily or 100 micrograms 3–4 times daily (in more severe cases, initially 600–800 micrograms daily);  
**CHILD** 50–100 micrograms 2–4 times daily or 100–200 micrograms twice daily  
Chronic asthma, by *aerosol inhalation* (high dose inhaler),  
**ADULT** 500 micrograms twice daily or 250 micrograms 4 times daily; if necessary may be increased to 500 micrograms 4 times daily;  
**CHILD** not recommended  
**Adverse effects:**  
Oropharyngeal candidosis, cough and dysphonia (usually only with high doses); adrenal suppression, growth retardation in children and adolescents, impaired bone metabolism, glaucoma and cataract (with high doses, but less frequent than with systemic corticosteroids); paradoxical bronchospasm—requires discontinuation and alternative therapy (if mild, may be prevented by inhalation of beta _2_ -adrenoceptor agonist or by transfer from aerosol to powder inhalation); rarely, urticaria, rash, angioedema  
**Candidosis.**  
Candidosis can be reduced by use of a spacing device (see notes above); rinsing the mouth with water after inhalation may help to prevent candidosis  

THEOPHYLLINE AND AMINOPHYLLINE

Aminophylline is a representative xanthine bronchodilator. Various drugs including theophylline can serve as alternatives

Tablets, theophylline 100 mg
Modified-release tablets, theophylline 125mg, 250 mg sustained release
Injection (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule

Uses:
Chronic asthma including nocturnal asthma; acute severe asthma

Precautions:
Cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses; interactions: Appendix 1

Contraindications:
Porphyria; known hypersensitivity to ethylenediamine (for aminophylline)

Dosage:
Chronic asthma, by mouth (as tablets), ADULT and CHILD over 12 years, 100–200 mg 3–4 times daily after food; by mouth (as modified-release tablets) ADULT 300–450 mg every 12 hours
Nocturnal asthma, by mouth (as modified-release tablets), ADULT total daily requirement as single evening dose

MONTELUKAST

Montelukast tabs 10mg

Uses: Prophylaxis and chronic treatment of asthma, relief of symptoms of seasonal allergic rhinitis in adults and children >2 years.

Precaution: Montelukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmatics. Should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Safety in children < 1 year of age has not been established.

Lactation: Excretion in breast milk unknown/use with caution

Chrug-Strauss syndrome

Adverse Reactions:
Gastrointestinal disturbances, dry mouth, thirst; hypersensitivity reactions including anaphylaxis, angioedema and skin reactions; asthenia, dizziness, irritability, restlessness, headache,
sleep disorders (insomnia, drowsiness, abnormal dreams, nightmares); upper respiratory tract infection, fever, arthralgia, myalgia; increase bleeding tendency, oedema and seizures

**Dose:**
- 10mg daily at bedtime;  
- **CHILD** 2-5 years: 4mg daily at bedtime, 6-14 years 5mg daily at bedtime

**IPRATROPIUM BROMIDE**

*Aerosol inhalation* (Pressurized inhalation), ipratropium bromide 20 micrograms/metered dose

**Uses:**
Chronic asthma; chronic obstructive pulmonary disease

**Precautions:**
Prostatic hypertrophy; pregnancy; glaucoma (standard doses unlikely to be harmful; reported with nebulized drug, particularly in association with nebulized salbutamol)

**Dosage:**
- Chronic asthma or chronic obstructive pulmonary disease, *by aerosol inhalation*, **ADULT** 20–40 micrograms, in early treatment up to 80 micrograms at a time, 3–4 times daily; **CHILD** up to 6 years, 20 micrograms 3 times daily, 6–12 years, 20–40 micrograms 3 times daily

**Adverse effects:**
Occasionally, dry mouth; rarely, urinary retention, constipation
SECTION 26
SOLUTIONS
CORRECTING WATER, ELECTROLYTE AND ACID-BASE DISTURBANCES

26.1 Oral electrolytes solution
   26.1.1 Oral Rehydration
   26.1.2 Oral potassium
   26.2 Parenteral
   26.3 Miscellaneous
26.1 Oral electrolyte solutions

26.1. Oral rehydration

Replacement of fluid and electrolytes orally can be achieved by giving oral rehydration salts—solutions containing sodium, potassium and glucose. Acute diarrhoea in children should always be treated with oral rehydration solution according to plans A, B, or C as shown.

Treatment of dehydration: WHO recommendations

According to the degree of dehydration, health professionals are advised to follow one of 3 management plans.

**Plan A: no dehydration.** Nutritional advice and increased fluid intake are sufficient (soup, rice, water and yoghurt, or even water). For infants aged under 6 months who have not yet started taking solids, oral rehydration solution must be presented before offering milk. Mother’s milk or dried cow’s milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of breastfeeding must be increased.

**Plan B: moderate dehydration.** Whatever the child’s age, a 4-hour treatment plan is applied to avoid short-term problems. Feeding should not therefore be envisaged initially. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution with a spoon 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 can be given if the child continues to have frequent stools. In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate (about one teaspoonful every 2 minutes). The child’s status must be re-assessed after 4 hours to decide on the most appropriate subsequent treatment. 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 most urgent priority is to start rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution must be given pending, and even during, intravenous infusion (20 ml/kg every hour by mouth before infusion, then 5 ml/kg every hour by mouth during intravenous rehydration. For intravenous supplementation, it is recommended that compound solution of sodium lactate (see section 26.2) is administered at a rate adapted to the child’s age (infant under 12 months: 30 ml/kg over 1 hour then 70 ml/kg over 5 hours; child over 12 months: the same amounts over 30 minutes and 2.5 hours respectively). If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution, at a rate of...
20 ml/kg every hour. If the child vomits, the rate of administration of the oral solution should be reduced.

**Oral rehydration salts**

*Glucose salt solution*

- sodium chloride 2.6 g/litre of clean water
- trisodium citrate 2.9 g/litre of clean water
- potassium chloride 1.5 g/litre of clean water
- glucose (anhydrous) 13.5 g/litre of clean water

When glucose and trisodium citrate are not available, they may be replaced:

- sucrose (common sugar) 27 g/litre of clean water
- sodium bicarbonate 2.5 g/litre 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.

**CHOLERA.**

In cases of cholera, oral rehydration salts containing a higher concentration of sodium may be required to prevent hyponatraemia.

**Uses:**
- Dehydration from acute diarrhoea

**Precautions:**
- Renal impairment

**Dosage:**
- Fluid and electrolyte loss in acute diarrhoea, *by mouth*, ADULT 200–400 ml solution after every loose motion; INFANT and CHILD according to Plans A, B or C (see above)

**Adverse effects:**
- Vomiting—may indicate too rapid administration; hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution

26.1.2 Oral potassium

Compensation for potassium loss is necessary in patients taking digoxin or antiarrhythmic drugs where potassium depletion
may induce arrhythmias. It is also necessary in patients with secondary hyperaldosteronism (renal artery stenosis, liver cirrhosis, the nephrotic syndrome, severe heart failure) and those with excessive loss of potassium in the faeces (chronic diarrhoea associated with intestinal malabsorption or laxative abuse).

Measures to compensate for potassium loss may also be required in the elderly since they often take inadequate amounts in the diet (but see warning on use in renal insufficiency, below). Measures may also be required during long-term administration of drugs known to induce potassium loss (for example, corticosteroids). Potassium supplements are seldom required with the small doses of diuretics given to treat hypertension. Potassium-sparing diuretics (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as furosemide or the thiazides when these are given to eliminate oedema (see section 16.3).

For the prevention of hypokalaemia doses of potassium chloride 2 to 4 g (approximately 25 to 50 mmol) daily by mouth are suitable in patients taking a normal diet. Smaller doses must be used if there is renal insufficiency (common in the elderly) otherwise there is a danger of hyperkalaemia. Larger doses may be required in established potassium depletion, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma potassium and specialist advice required).

Potassium depletion is frequently associated with metabolic alkalosis and chloride depletion and these disorders require correction.

**POTASSIUM CHLORIDE**

*Powder for oral solution*, potassium chloride 1.5 g (potassium 20 mmol, chloride 20 mmol)

**Uses:**
Prevention and treatment of hypokalaemia (see notes above)

**Contraindications:**
Severe renal impairment; plasma potassium concentration above 5 mmol/litre

**Precautions:**
elderly, mild to moderate renal impairment (close monitoring required, Appendix 4), history of peptic ulcer; **important:** special hazard if given with drugs liable to raise plasma potassium concentrations such as potassium-sparing diuretics, ACE inhibitors or ciclosporin, for other interactions: Appendix 1

**Dosage:**
Prevention of hypokalaemia (see notes above), *by mouth*,

ADULT 20–50 mmol daily after meals
Potassium depletion (see notes above), by mouth, ADULT 40–100 mmol daily in divided doses after meals: adjust dose according to severity of deficiency and any continuing loss of potassium reconstitution and administration.
According to manufacturer’s directions
Adverse effects:
Nausea and vomiting, gastrointestinal irritation

26.2 Parenteral electrolyte solutions

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated or vomiting and is unable to take adequate amounts by mouth. The nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination of each individual. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance.
Isotonic solutions may be infused safely into a peripheral vein. More concentrated solutions, for example 20% glucose, are best given through an indwelling catheter positioned in a large vein.

Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentrations and is indicated in sodium depletion which may arise from conditions such as gastroenteritis, diabetic ketoacidosis, ileus and ascites. In a severe deficit of from 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 hours; thereafter infusion can usually be at a slower rate. Excessive administration should be avoided; the jugular venous pressure should be assessed; the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.
Chronic hyponatraemia should ideally be managed by fluid restriction. However, if sodium chloride is required, the deficit should be corrected slowly to avoid risk of osmotic demyelination syndrome; the rise in plasma-sodium concentration should be limited to no more than 10 mmol/litre in 24 hours. The more physiologically appropriate compound solution of sodium lactate can be used instead of isotonic sodium chloride solution during surgery or in the initial management of the injured or wounded.

Sodium chloride and glucose solutions are indicated when

there is combined water and sodium depletion. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na+ remains extracellular. Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

**Glucose** solutions (5%) are mainly used to replace water deficits and should be given alone when there is no significant loss of electrolytes. Average water requirement in a healthy adult are 1.5 to 2.5 litres daily and this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake, as for example may occur in coma or dysphagia or in the aged or apathetic who may not drink water in sufficient amount on their own initiative. Excessive loss of water without loss of electrolytes is uncommon, occurring in fevers, hyperthyroidism, and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia. The volume of glucose solution needed to replace deficits varies with the severity of the disorder, but usually lies within the range of 2 to 6 litres. Glucose solutions are also given in regimens with calcium, bicarbonate, and insulin for the emergency treatment of hyperkalaemia. They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuing insulin infusion. If glucose or sugar cannot be given orally to treat hypoglycaemia, glucose 50% may be given intravenously into a large vein through a large-gauge needle; this concentration is very irritant on extravasation and it is also viscous and difficult to administer. Larger volumes of less concentrated glucose solutions (10% or 20%) can be used as alternatives and are less irritant.

**Sodium hydrogen carbonate** (sodium bicarbonate) is used to control severe metabolic acidosis (as in renal failure). Since this condition is usually attended by sodium depletion, it is reasonable to correct this first by the administration of isotonic sodium chloride intravenous infusion, provided the kidneys are not primarily affected and the degree of acidosis is not so severe as to impair renal function. In these circumstances, isotonic sodium chloride alone is usually effective as it restores the ability of the kidneys to generate bicarbonate. In renal acidosis or in severe metabolic acidosis of any origin, for example blood pH < 7.1, sodium hydrogen carbonate (1.4%)
may be infused with isotonic sodium chloride when the acidosis remains unresponsive to correction of anoxia or fluid depletion; a total volume of up to 6 litres (4 litres of sodium chloride and 2 litres of sodium hydrogen carbonate) may be necessary in the adult. In severe shock due for example to cardiac arrest, metabolic acidosis may develop without sodium depletion; in these circumstances sodium hydrogen carbonate is best given in a small volume of hypertonic solution (for example 50 ml of 8.4% solution intravenously); plasma pH should be monitored. Sodium hydrogen carbonate is also used in the emergency management of hyperkalaemia.

Intravenous potassium chloride in sodium chloride infusion is the initial treatment for the correction of severe hypokalaemia when sufficient potassium cannot be taken by mouth. Potassium chloride concentrate may be added to sodium chloride 0.9% infusion, thoroughly mixed, and given slowly over 2 to 3 hours with specialist advice and ECG monitoring in difficult cases. Repeated measurements of plasma potassium are necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia which is especially likely to occur in renal impairment. Initial potassium replacement therapy should not involve glucose infusions because glucose may cause a further decrease in the plasma-potassium concentration.

GLUCOSE

*Infusion* (Solution for infusion), glucose 5% (iso-osmotic), 10% (hyperosmotic), 50% (hyperosmotic)

**Uses:**
Fluid replacement without significant electrolyte deficit (see notes above); treatment of hypoglycaemia

**Precautions:**
Diabetes mellitus (may require additional insulin)

**Dosage:**
Fluid replacement, by intravenous infusion, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above)

Treatment of hypoglycaemia, by intravenous infusion of 50% glucose solution into a large vein, ADULT, 25 ml (see also notes above)

**Adverse effects:**
Glucose injections, especially if hypertonic, may have a low pH and cause venous irritation and thrombophlebitis; fluid and electrolyte disturbances; oedema or water intoxication (on prolonged administration or rapid infusion of large volumes of isotonic solutions); hyperglycaemia (on prolonged administration of hypertonic solutions)

SODIUM CHLORIDE

Infusion (Solution for infusion), sodium chloride 0.9% (9 g, 154 mmol each of Na⁺ and Cl⁻ /litre)

Uses:
Electrolyte and fluid replacement

Precautions:
Restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, peripheral and pulmonary oedema, and toxaemia of pregnancy

Dosage:
Fluid and electrolyte replacement, by intravenous infusion, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above)

Adverse effects:
Administration of large doses may give rise to sodium accumulation and oedema

SODIUM LACTATE, COMPOUND SOLUTION OF

Compound solution of sodium lactate is a representative intravenous electrolyte solution. Various solutions can serve as alternatives

Infusion (Solution for infusion), sodium chloride 0.6%, sodium lactate 0.25%, potassium chloride 0.04%, calcium chloride 0.027% (containing Na⁺ 131 mmol, K⁺ 5 mmol, Ca²⁺ 2 mmol, HCO₃⁻ (as lactate) 29 mmol, Cl⁻ 111 mmol/litre)

Uses:
Pre- and perioperative fluid and electrolyte replacement; hypovolaemic shock

Contraindications:
Metabolic or respiratory alkalosis; hypocalcaemia or hypochlorhydria

Precautions:
Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, and toxaemia of pregnancy; interactions: Appendix 1

Dosage:
Fluid and electrolyte replacement or hypovolaemic shock, by intravenous infusion, ADULT and CHILD determined on the basis of clinical and, whenever possible, electrolyte monitoring (see notes above)

Adverse effects:
Excessive administration may cause metabolic alkalosis; administration of large doses may give rise to oedema
SODIUM HYDROGEN CARBONATE

Infusion (Solution for infusion), sodium hydrogen carbonate 1.4% (14 g, 166.7 mmol each of Na⁺ and HCO₃⁻ /litre)

Injection (Solution for injection), sodium hydrogen carbonate 8.4% (840 mg, 10 mmol each of Na⁺ and HCO₃⁻ /10 ml)

Uses:
Metabolic acidosis

Contraindications:
Metabolic or respiratory alkalosis, hypocalcaemia, hypochlo-rydia

Precautions:
Restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, peripheral and pulmonary oedema, tox-aeemia of pregnancy; monitor electrolytes and acid-base status;

interactions: Appendix 1

Dosage:
Metabolic acidosis, by slow intravenous injection, ADULT and CHILD a strong solution (up to 8.4%) or by continuous intravenous infusion, ADULT and CHILD a weaker solution (usually 1.4%), an amount appropriate to the body base deficit (see notes above)

Adverse effects:
Excessive administration may cause hypokalaemia and meta-bolic alkalosis, especially in renal impairment; large doses may give rise to sodium accumulation and oedema

POTASSIUM CHLORIDE

Concentrate for infusion (Concentrate for solution for infusion), potassium chloride 11.2% (112 mg, approximately 1.5 mmol each of K⁺ and Cl⁻ /ml), 20-ml ampoule

Uses:
Electrolyte imbalance; see also oral potassium (section 26.1.2)

Precautions:
For intravenous infusion the concentration of solution should not usually exceed 3.2 g (43 mmol)/litre; specialist advice and ECG monitoring (see notes above); renal impairment (Appendix 4); interactions: Appendix 1

Dosage:
Electrolyte imbalance, by slow intravenous infusion, ADULT and CHILD depending on the deficit or the daily maintenance requirements (see also notes above) dilution and administration. Must be diluted and thoroughly mixed before use and administered according to manufac-turer’s directions

Adverse effects:

Cardiac toxicity on rapid infusion
Oral Rehydrating Salt
See section 17.7.1
Hypokalial
Injection, IV 250mls

26.3 Water

**Water for injections**

*Injection*, sterile distilled water free from pyrogens, 2-ml, 5-ml, 10-ml ampoules

**Uses:**
in preparations intended for parenteral administration and in other sterile preparations
SECTION 27
VITAMINS AND MINERALS

27.1. Vitamins
27.2. Minerals
27. Vitamins

Vitamins are used for the prevention and treatment of specific deficiency states or when the diet is known to be inadequate. It has often been suggested but never convincingly proved, that subclinical vitamin deficiencies cause much chronic ill-health and liability to infections. This has led to enormous consumption of vitamin preparations, which have no more than placebo value. Most vitamins are comparatively non-toxic but prolonged administration of high doses of retinol (vitamin A), ergocalciferol (vitamin D₃) and pyridoxine (vitamin B₆) may have severe adverse effects.

Retinol (vitamin A) is a fat-soluble substance stored in body organs, principally the liver. Periodic high-dose supplementation is intended to protect against vitamin A deficiency which is associated with ocular defects particularly xerophthalmia (including night blindness which may progress to severe eye lesions and blindness), and an increased susceptibility to infections, particularly measles and diarrhoea. Universal vitamin A distribution involves the periodic administration of supplemental doses to all preschool-age children with priority given to age groups, 6 months to 3 years, or regions at greatest risk. All mothers in high-risk regions should also receive a high dose of vitamin A within 8 weeks of delivery. Since vitamin A is associated with a teratogenic effect it should be given in smaller doses (no more than 10,000 units/day) to women of child-bearing age. It is also used in the treatment of active xerophthalmia. Doses of vitamin A should be administered orally immediately upon diagnosis of xerophthalmia and thereafter patients with acute corneal lesions should be referred to a hospital on an emergency basis. In women of child-bearing age there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant with the serious consequences of xerophthalmia. Where there are severe signs of xerophthalmia high dose treatment as for patients over 1 year should be given. When less severe symptoms are present (for example night blindness) a much lower dose is recommended. Vitamin A therapy should also be given during epidemics of measles to reduce complications.

Vitamin B is composed of widely differing substances which are, for convenience, classed as ‘vitamin B complex’. Thiamine (vitamin B₁) is used orally for deficiency due to inadequate dietary intake. Severe deficiency may result in ‘beri-beri’. Chronic dry ‘beri-beri’ is characterized by peripheral neuropathy, muscle wasting and weakness, and paralysis; wet ‘beri-beri’ is characterized by cardiac failure and oedema. Wernicke-Korsakoff syndrome (demyelination of the CNS) may develop in severe deficiency. Thiamine is given by intravenous injection.
in doses of up to 300 mg daily (parenteral preparations may contain several B group vitamins) as initial treatment in severe deficiency states. Potentially severe allergic reactions may occur after parenteral administration. Facilities for resuscitation should be immediately available. **Riboflavin (vitamin B₂)** deficiency may result from reduced dietary intake or reduced absorption due to liver disease, alcoholism, chronic infection or probenecid therapy. It may also occur in association with other deficiency states such as pellagra. **Pyridoxine (vitamin B₆)** deficiency is rare as the vitamin is widely distributed in foods, but deficiency may occur during isoniazid therapy and is characterized by peripheral neuritis. High doses are given in some metabolic disorders, such as hyperoxaluria and it is also used in sideroblastic anaemia. **Hydroxocobalamin** is the form of vitamin B₁₂ used to treat vitamin B₁₂ deficiency due to dietary deficiency or malabsorption (see section 10.1).

**Folic acid** is essential for the synthesis of DNA and certain proteins. Deficiency of folic acid or vitamin B₁₂ is associated with megaloblastic anaemia. Folic acid should not be used in undiagnosed megaloblastic anaemia unless vitamin B₁₂ is administered concurrently, otherwise neuropathy may be precipitated (see section 10.1). Supplementation with folic acid 400 micrograms daily is recommended for women of child-bearing potential in order to reduce the risk of serious neural tube defects in their offspring (see section 10.1).

**Ascorbic acid** (vitamin C) is used for the prevention and treatment of scurvy. Claims that ascorbic acid is of value in the treatment of common colds are unsubstantiated.

The term **vitamin D** covers a range of compounds including **ergocalciferol** (vitamin D₂) and **colecalciferol** (vitamin D₃). These two compounds are equipotent and either can be used to prevent and treat rickets.

Simple deficiency of vitamin D occurs in those who have an inadequate dietary intake or who fail to produce enough colecalciferol (vitamin D₃) in their skin from the precursor 7-dehydrocholesterol in response to ultraviolet light. Children with dark skin must continue vitamin D prophylaxis for up to 24 months because of their inability to produce enough vitamin D₃ in their skin. Dark skin with high melanin content must be exposed to daylight longer than light skin in order to obtain the same synthesis of vitamin D₃. Vitamin D is also used in deficiency states caused by intestinal malabsorption or chronic liver disease and for the hypocalcaemia of hypoparathyroidism.

**Vitamin K** is necessary for the production of blood clotting factors (see section 10.2).
PYRIDOXINE HYDROCHLORIDE

Vitamin B₆
Tablets, pyridoxine hydrochloride 50 mg

Uses:
Treatment of pyridoxine deficiency due to metabolic disorders; isoniazid neuropathy; sideroblastic anaemia

Precautions:

Interactions: Appendix 1

Dosage:
Deficiency states, by mouth, ADULT 25–50 mg up to 3 times daily
Isoniazid neuropathy, prophylaxis, by mouth, ADULT 10 mg daily
Isoniazid neuropathy, treatment, by mouth, ADULT 50 mg 3 times daily
Sideroblastic anaemia, by mouth, ADULT 100–400 mg daily in divided doses

Adverse effects:
Generally well tolerated, but chronic administration of high doses may cause peripheral neuropathies

Vitamin B complex

Parenteral Injection, IM, Vitamin B, compound, nicotinamide 15mg, riboflavin 1mg, thiamine hydrochloride 1mg

Use:
Treatment of vitamin B deficiency, rapid correction of severe depletion or malabsorption (e.g. in alcoholism, after acute infections, postoperatively, or in psychiatric states); neuropathies

RETINOL

Vitamin A
Sugar-coated tablets (Coated tablets), retinol (as palmitate) 10 000 units
Capsules, retinol (as palmitate) 200 000 units
Oral solution (oily), retinol (as palmitate) 100 000 units/ml
Water-miscible injection (Solution for injection), retinol (as palmitate) 50 000 units/ml, 2-ml ampoule

Uses:
Prevention and treatment of vitamin A deficiency; prevention of complications of measles

Precautions:
pregnancy (teratogenic; see notes above and Appendix 2); breastfeeding (Appendix 3)

Dosage:
Prevention of vitamin A deficiency (universal or targeted distribution programmes), by mouth, INFANT under 6 months,
50 000 units, 6–12 months, 100 000 units every 4–6 months, preferably at measles vaccination; CHILD over 1 year (pre-school), 200 000 units every 4–6 months; ADULT, 200 000 units every 6 months; ADULT pregnant woman, maximum of 10 000 units daily or maximum 25 000 units weekly; ADULT mothers, 200 000 units at delivery or within 6 weeks

Treatment of xerophthalmia, by mouth, INFANT under 6 months, 50 000 units on diagnosis, repeated 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 over 1 year and ADULT (except woman of child-bearing age) 200 000 units on diagnosis, repeated next day and then after 2 weeks; ADULT (woman of child-bearing age, see notes above), severe signs of xerophthalmia, as for other adults; less severe cases (for example, night blindness), 5000–10 000 units daily for at least 4 weeks or up to 25 000 units weekly

Note.
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

Adverse effects:
no serious or irreversible adverse effects in recommended doses; high intake may cause birth defects; transient increased intracranial pressure in adults 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

HYDROXOCOBALAMIN-VIT B12

Injection, 10ml

Use
Treatment of pernicious anemia, vit B12 deficiency, increased vitB12 requirements due to pregnancy, thyrotoxicosis, haemorrhage, malignancies,, liver or kidney disease., neuropathies

Contraindications
Patients with hereditary optic nerve atrophy

Precautions
Avoid in premature infants
Adverse effects
Itching, diarrhea

Dosage
Vitamin B12 deficiency: I.M:
CHILDREN: 1-5mg given in single dose or 100mcg given over two weeks, followed 30 – 50 mcg/month
ADULTS: 30mcg/day for 5-10days, followed by 100-200mcg/

RIBOFLAVIN

Vitamin B<sub>2</sub> Tablets, riboflavin 5 mg

Uses:
vitamin B<sub>2</sub> deficiency

Dosage:
Treatment of vitamin B<sub>2</sub> deficiency, by mouth, ADULT and child up to 30 mg daily in divided doses
Prophylaxis of vitamin B<sub>2</sub> deficiency, by mouth, ADULT and child 1–2 mg daily

THIAMINE HYDROCHLORIDE

Vitamin B<sub>1</sub> Tablets, thiamine hydrochloride 50 mg
Injection, 100mg/ml

Uses:
prevention and treatment of vitamin B<sub>1</sub> deficiency

Precautions:
parenteral administration (see notes above); breastfeeding (Appendix 3)

Dosage:
Mild chronic thiamine deficiency, by mouth, ADULT 10–25 mg daily
Multivitamins
Tablets, Chewable tablets, Syrup

Use
Dietary supplement

Contraindications
Hypersensitivity to any component of the formulation, pre-existing hypervitaminosis

Precautions
Use with caution in patients with severe renal or liver failure

Adverse effects
Hypervitaminosis, allergic reactions

Dosage

CHILD Oral:
d" 2 years: Drops: 1ml/day
e" 2 years: Chew 1 tablet/day
e"4 years: 5ml/day liquid

ADULTS:
Oral: 1 tablet/day or 5ml liquid

27.2 Minerals

Calcium gluconate, Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary

requirement varies with age and is relatively greater in childhood, pregnancy and lactation due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended daily amount reduces the rate of bone loss. In hypocalcaemic tetany calcium gluconate must be given parenterally but plasma calcium must be monitored. Calcium gluconate is also used in cardiac resuscitation.

Iodine is among the body’s essential trace elements. The recommended intake of iodine is 150 micrograms daily (200 micrograms daily in pregnant and breastfeeding women); in children the recommended intake of iodine is 50 micrograms daily for infants under 1 year, 90 micrograms daily for children aged 2–6 years, and 120 micrograms daily for children aged 7–12 years. Deficiency causes endemic goitre and results in endemic cretinism (characterized by deaf-mutism, intellectual deficit, spasticity and sometimes hypothyroidism), impaired mental function in children and adults and an increased incidence of still-births and perinatal and infant mortality. Iodine and iodides may suppress neonatal thyroid function and in general iodine compounds should be avoided in pregnancy. Where it is essential to prevent neonatal goitre and cretinism, iodine should not be withheld from pregnant women. Control of iodine deficiency largely depends upon salt iodization with potassium iodide or potassium iodate and through dietary diversification.

**CALCIUM GLUCONATE**

Calcium gluconate is a complementary drug

*Injection (Solution for injection), calcium gluconate (monohydrate) 100 mg (Ca\(^{2+}\) 220 micromol)/ml, 10-ml ampoule

Tablet, 300mg

**Uses:**
Treatment and prevention of hypocalcemia; hypocalcaemic tetany, cardiac disturbances of hyperkalemia, cardiac resuscitation when epinephrine fails to improve myocardial contractility; calcium supplement, calcium channel blocker toxicity

**Contraindications:**
conditions associated with hypercalcaemia and hypercalciuria (for example some forms of malignant disease)

**Precautions:**
monitor plasma calcium concentration; **interactions:** Appendix 1

**Dosage:**
Hypocalcaemic tetany, by *slow intravenous injection*, **ADULT**
1 g (2.2 mmol) followed by *continuous intravenous infusion* of about 4 g (8.8 mmol) daily

**Children:** Usually require half the adult dose

**CALCIUM SALT**

Calcium Carbonate  20 mEq OR 400mg  
Calcium Lactate  6 mEq or 135mg  
Calcium Gluconate  4 mEq or 90mg  

For elemental calcium:  
**ADULTS and CHILDREN** 1-10 years old:  
40 mEq or 800mg  
Pregnant/lactating women and children 10-18 years old: 60mEq or 1200mg  

**Dilution and administration.**  
According to manufacturer’s directions  

**Adverse effects:**  
mild gastrointestinal disturbances; bradycardia, arrhythmia; irritation at injection site  

**IODINE**

*Oily injection* (Solution for injection), iodine (as iodized oil) 480 mg/ml. 0.5-ml ampoule, 1-ml ampoule  

**Note.**  
Iodized oil may also be given by mouth  

**Uses:**  
prevention and treatment of iodine deficiency  

**Contraindications:**  
breastfeeding (Appendix 3)  

**Precautions:**  
over 45 years old or with nodular goitre (especially susceptible to hyperthyroidism when given iodine supplements—iodized oil may not be appropriate); may interfere with thyroid-function tests; pregnancy (see notes above and Appendix 2)  

**Dosage:**  
Endemic moderate to severe iodine deficiency, *by intramuscular injection*, **ADULT** women of child-bearing age, including any stage of pregnancy, 480 mg once each year; *by mouth*, **ADULT** during pregnancy and one year postpartum, 300–480 mg once a year or 100–300 mg every 6 months; women of child-bearing age, 400–960 mg once a year or 200–480 mg every 6 months  

Iodine deficiency, *by intramuscular injection*, **INFANT** up to 1 year, 190 mg; **CHILD** and **ADULT** 380 mg (aged over 45 years or with nodular goitre, 76 mg but see also Precautions) (provides up to 3 years protection)  

Iodine deficiency, *by mouth*, **ADULT** (except during pregnancy) and **CHILD** above 6 years, 400 mg once a year; **ADULT** during pregnancy, single dose of 200 mg; **INFANT** under 1 year, single dose of 100 mg; **CHILD** 1–5 years, 200 mg once a year  

27.2 Minerals

**Adverse effects:**
hypersensitivity reactions; goitre and hypothyroidism; hyperthyroidism

B-Complex tablets and Injections