1. Analgesics, Antipyretics, Non-Steroidal Anti-Inflammatory Drugs

Analgesics are used to relieve/reduce body pain and antipyretics are used to reduce elevated body temperature. Non-opioid analgesics are particularly suitable for relieveing or management of pain in musculoskeletal conditions whereas the opioid analgesics are more suitable for moderate to severe visceral pain. Those non-opioid analgesics which also have anti-inflammatory actions include salicylates and NSAIDs; 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. The pain and inflammation of an acute attack of gout is treated with a NSAID or colchicine; a xanthine-oxidase inhibitor is used for long-term control of gout. Neurogenic pain generally responds poorly to conventional analgesics; treatment can be difficult and includes the use of carbamazepine for trigeminal neuralgia and amitriptyline for diabetic neuropathy and post-therapeutic neuralgia.

1.1 Non-Opioid, Non-Steroidal Anti-Inflammatory Drugs

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.

Acetylsalicylic Acid* (Refer Page No. 281 and 317)

Pregnancy Category-D

Indications	*Management of mild to moderate pain such as headache, acute migraine attacks,transient musculoskeletal pain, dysmenorrhoeal pain and for reducing fever; pain and inflammation of rheumatoid arthritis; antiplatelet agent for prophylaxis of myocardial infarction, stable angina pectoris; stroke prophylaxis.*
Availability	**TABLETS** 50, 60, 75, 80, 150, 300 and 325 mg.
Dose	***Oral***
	Adult- Analgesic and antipyretic including migraine attacks: 0.3 to 0.9g, 3 to 4 times a day (max. 4g daily). Acute Rheumatic fever: 4 to 6g or 75 to 100 mg/kg daily in divided doses. Antiplatelet: 75-325 mg/day .
	Child- Under 16 years: not recommended (can cause Reye's syndrome).
Contraindications	Hypersensitivity (including asthma; angioedema; urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (may cause Reye's syndrome); gastrointestinal ulceration; haemophilia and other bleeding disorders; not for treatment of gout; severe renal or hepatic impairment; lactation. It is known to cause haemolytic anaemia in people who have the genetic disease- G-6-PD-deficiency.
Precautions	Asthma, allergic disease; impaired renal or hepatic function (Appendices 7d and 7a); lactation (Appendix 7b); pregnancy (Appendix 7c); elderly; G-6-PD-deficiency; dehydration; interactions (Appendix 6a, 6c, 6d).

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, blood disorders (particularly thrombocytopenia); rarely, oedema; myocarditis; Reye's syndrome.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Diclofenac

Pregnancy Category-B

Schedule H

Indications *Acute musculo-skeletal pain; arthritis; gout; spondylitis; migraine; post-operative pain.*

Availability **TABLETS** 25 and 50 mg Plain; 75 and 100 mg SR; **CAPSULES** 100 mg, 100 mg CR; **INJECTION** 3 ml ampoule (25 mg/ml); **EYE/EAR DROPS** 0.1% w/v; **SUPPOSITORIES** 25, 50 and 100 mg; **GEL** 1%w/w.

Dose

Oral

100 to 150 mg daily in 2 to 3 divided doses, (max 150 mg/day) maintenance by 50 to 100 mg in divided doses.

Intramuscular injection

75 mg, 2 to 3 times daily.

Topically

Adult- Apply 1% w/w gel on to affected area 3 to 4 times daily.

Instill to eye

Post-operative ocular inflammation:

Adult- as sodium (1% w/v), 4 times daily starting 24 h after surgery for up to 28 days.

Rectal

Post-operative pain.

Adult- 75 to 150 mg daily in divided doses (max. 150 mg/day, inclusive of diclofenac administered through other routes). **Child-** 6 to 12 year: 1 to 2 mg/kg/day in divided doses for max. of 4 days.

Contraindications Porphyria; avoid injections containing benzyl alcohol in neonates; history of gastric ulcers, bleeding or perforation.

Additional contraindications include concomitant NSAID or anticoagulant use (including low-dose heparin); history of haemorrhagic diathesis; history of confirmed or suspected cerebrovascular bleeding; operations with high risk of haemorrhage; history of asthma; moderate or severe renal impairment; hypovolaemia; dehydration.

Precautions NSAIDs should be used with caution in the elderly (risk of serious side-effects and fatalities); interactions (Appendix 6a, 6c, 6d); pregnancy (Appendix 7c); patients with coagulation disorders; hepatic, renal and cardiac impairment; history of gastrointestinal lesions.

Adverse Effects Injection site reactions; transient epigastric pain, risk of thrombotic events; toxic epidermal necrolysis; Abnormality in kidney function.

Storage Store protected from light.

Ibuprofen*

Pregnancy Category-C

Schedule H

Indications *Pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis; mild to moderate pain including dysmenorrhoeal pain, headache; pain in children; acute migraine attack.*

Availability **TABLETS** 200, 400 and 600 mg; **CAPSULES** 400 mg Plain, 300 mg SR; **SUSPENSION** 100 mg/5 ml.

Dose ***Oral***

Adult- and Child over 12 years- initially 300 to 400 mg 3 to 4 times daily, increase if necessary (max. 2.4g daily), maintenance dose of 0.6 to 1.2g daily may be adequate.

Infant or Child over 3 months- 5-10 mg/kg 3 to 4 times/day, Maximum daily dose: 40 mg/kg/day.

Intravenous injection and infusion

Neonate- initially by intravenous injection (over atleast 5 min) 25-100 µg/kg then by continuous intravenous infusion 5-40 µg/kg/h. adjusted according to response.

Child- 1-6 months: initially by intravenous injection (over atleast 5 min) 100-200 µg/kg then by continous infusion 10-30 µg/h. adjusted according to response.
6 months-12 years: initially by intravenous injection (over atleast 5 min) 100-200 µg/kg, adjusted according to response. Juvenile rheumatoid arthritis: 20 to 40 mg/kg/day in 3 to 4 divided doses.

Contraindications Hypersensitivity (including asthma; angioedema; urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration; for treatment of pre-operative pain in the setting of coronary artery bypass graft surgery; neonates with congenital heart disease.

Precautions Renal and hepatic impairment (Appendix 7a); preferably avoid if history of peptic ulceration; cardiac disease; elderly; pregnancy (Appendix 7c); lactation (Appendix 7b); coagulation defects; allergic disorders; interactions (Appendix 6a, 6c, 6d).

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; renal failure; fluid retention (rarely, precipitating congestive heart failure in elderly), raised blood pressure; rarely, hepatic damage; alveolitis, pulmonary eosinophilia; pancreatitis; visual disturbances; erythema multiforme (Stevens-Johnson syndrome); toxic dermal necrolysis (Lyell's syndrome); colitis; aseptic meningitis. Skin reactions like dermatitis.

Storage Store protected from light and moisture.

Mefenamic Acid

Pregnancy Category-C

Indications *Treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, mild to moderate pain, inflammation, fever dental pain.*

Availability **TABLETS** 100 mg, 250 mg, 500 mg. **CAPSULES** 250 mg. **SUSPENSION** 50 mg/5 ml.

Dose ***Adult***

Pain: 500 mg orally, followed by 250 mg every 6 hours as needed, not to exceed 7 days.
Dysmenorrhea: 500 mg orally, followed by 250 mg every 6 hours starting with the onset of menses.
Children
Pain: 14 to 18 years: 500 mg orally followed by 250 mg every 6 hours as needed, not to exceed 7 days.

Contraindications Known hypersensitivity to mefenamic acid; patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs; peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery, active ulceration or chronic inflammation of the gastrointestinal tract, pre-existing renal disease, pregnancy (Appendix 7c), interactions (Appendix 6c).

Precautions Hepatic effects: Borderline elevations of one or more liver function tests may occur. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), the drug should be discontinued.
Anaemia: Patients on long-term treatment should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anaemia.
Asthma: Mefenamic acid should not be administered to patients with aspirin sensitive asthma and should be used with caution in patients with preexisting asthma.

Adverse Effects Gastrointestinal experiences including-abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding/ perforation, heartburn, nausea, gastrointestinal ulcers, vomiting, abnormal renal function, bronchospasm, anaemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus.

Storage Store protected from light and moisture.

Paracetamol*

Pregnancy Category-B

Indications *Mild to moderate pain including dysmenorrhoeal pain, headache; pain relief in osteoarthritis and soft tissue lesions; pyrexia including post-immunisation pyrexia; acute migraine attack.*

Availability

TABLETS 500 and 650 mg Plain; 750 mg DT; **SYRUPS/SUSPENSION** 125 and 250 mg/5 ml; **INJECTION** 2 ml ampoule 125 mg/ml.; Intravenous infusion 500 mg and 1g.

Dose

Oral

Adult- 0.5 to 1g every 4 to 6 h (max. 4g, max 2g in alcoholics per day).

Child- for post-immunisation pyrexia, up to 2 months: 60 mg. 3 month to 1 year: 60 to 120 mg every 4 to 6 h. 1 to 5 years: 120 to 250 mg every 4 to 6 h. 6 to 12 years: 250 to 500 mg every 4 to 6 h.

Intramuscular injection

Adult- 250 mg every 4 to 6 h or as required.

Intravenous infusion

Adult- 1g every 6 hours, maximum daily dose 4 g.

Child- 15 mg/kg upto 4 times a day, maximum daily dose 60 mg/kg.

Precautions

Hepatic impairment (Appendix 7a); renal impairment; alcohol dependence; lactation (Appendix 7b); pregnancy (Appendix 7c); overdosage: chapter 7.2; interactions (Appendix 6a); G-6-PD deficiency.

Adverse Effects

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

Storage

Store protected from light and moisture.

1.2 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. 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.

Codeine* (Refer Page No. 72)

(Controlled Medicine Under the Narcotic Drugs and Psychotropic Substances Act 1985)

Pregnancy Category-C

Schedule H

Indications	*Mild to moderate pain; diarrhoea; cough suppressant; irritable bowel syndrome.*
Availability	**TABLET** 10 mg; **SYRUP** 15 mg/5 ml.
Dose	***Oral*** **Adult-** 30 to 60 mg every 4 h. (max. 240 mg/day). **Child-** 1 year to 12 year: 3 mg/kg daily in divided doses.
Contraindications	Respiratory depression; obstructive airways disease; acute asthma attack; where risk of paralytic ileus; hypersensitivity; head injury; increased intracranial pressure.
Precautions	Hepatic impairment (Appendix 7a) and renal impairment; opioids dependence; lactation; overdosage: chapter 7.2; pregnancy (Appendix 7c); interactions (Appendix 6c); hypothyroidism; shock.

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; orthostatic hypotension; respiratory depression; rhabdomyolysis; convulsions (especially in children).

Morphine* (Refer Page No. 422)

(Controlled Medicine Under the Narcotic Drugs and Psychotropic Substances Act, 1985)

Pregnancy Category-C

Schedule H, X

Indications

In severe pain (acute and chronic); myocardial infarction, acute pulmonary oedema; adjunct during major surgery and postoperative analgesia; prolonged relief of severe and intractable pain.

Availability

INJECTION 10 ml ampoule (1 mg/ml, 10 mg/ml, 15 mg/ml); **TABLETS** 10, 20, 30 and 60 mg.

Dose

Subcutaneous or intramuscular injection

Adult- Acute pain: 10 mg every 4 h.

Elderly or frail- Acute pain: 5 mg, adjust according to response (not suitable for patients having oedema).

Child- Acute pain: can be given to children in dose range of 0.2 to 0.8 mg/kg every 12 h. After 1 to 6 months: initially 100 to 200 µg/kg every 6 h, 2 to 12 years: initially 200 µg/kg every 4 h, 12 to 18 years: initially 2.5 to 10 mg every 4 h.

Slow intravenous injection

Adult- Acute pain: 2.5 mg every 4 h. Myocardial infarction: 10 mg (2 mg/min), followed by another 5 to 10 mg if necessary.

Elderly or frail- Acute pain: reduced dose.

Child- 0.1-0.15 mg/kg

Subcutaneous or intramuscular injection

Premedication: up to 10 mg, 1 to 1.5 h before operation.

Oral or subcutaneous or intramuscular injection

Chronic acute pain: 5 to 20 mg every 4 h or as per recovery (not suitable for patient having oedema).

Contraindications Acute respiratory depression, obstructive airway disease; 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 pheochromocytoma.

Precautions Renal and hepatic impairment (Appendix 7a); reduce dose or avoid in elderly and debilitated; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders, seizure disorder; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; pregnancy (Appendix 7c) and lactation (Appendix 7b); overdosage: chapter 7.2; interactions (Appendix 6a, 6c, 6d); driving and operating machinery.

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

Storage Store protected from light and moisture.

Pentazocine

Pregnancy Category-C

Indications *Moderate to severe pain; pre-anaesthetic medication; colic; trauma; surgical procedures; burns.*

Availability **TABLETS** 25 mg Plain, Combination: Paracetamol 500 mg + Pentazocine 15 mg; **INJECTION** 1 ml ampoule (30 mg/ml).

Dose ***Oral***

Adult- Pentazocine 50 mg every 3 to 4 h preferably after food (range 25 to 100 mg, max. 600 mg daily).

Child- 6 to 12 years: 25 mg.

Subcutaneous, intramuscular or intravenous injection

Adult- Moderate pain: 30 mg. Severe pain: 45 to 60 mg every 3 h to 4 h when necessary.

Child (Over 1 year)- by subcutaneous or intramuscular injection: 1 mg/kg; by intravenous injection: 500 µg/kg.

Contraindications Patients dependent on opioids; arterial or pulmonary hypertension; heart failure; narcotic dependence; hypersensitivity; ischaemia; myocardial infarction.

Precautions Avoid in porphyria; interactions (Appendix 6a); impaired respiratory function; pregnancy (Appendix 7c); renal or hepatic function; thyroid dysfunction; biliary tract impairment.

Adverse Effects Nausea, vomiting; euphoria, sedation, occasional hallucinations.

Storage Store protected from light and moisture.

Tramadol*

Pregnancy Category-C

Schedule H

Indications *Moderate or severe pain, post operative pain, in patients contraindicated to NSAIDs.*

Availability **TABLETS** 50 mg and 100 mg SR; **CAPSULE** 50 and 100 mg SR; **INJECTION** 1 and 2 ml ampoule (50 mg/ml).

Dose **Adult-** Moderate to severe pain: 50 to 100 mg, 4 to 6 hourly (max 400 mg/day).

Post operative pain: 100 mg i.v. initially followed by 50 mg every 10 to 20 min upto max. of 250 mg in the 1st h. Maintenance dose 50 to 100 mg, 4 to 6 hourly (max 600 mg/day).

Contraindications Patients with suicidal tendency; raised intracranial pressure; severe renal impairment; acute alcoholism; lactation.

Precautions Renal or hepatic impairment; history of epilepsy; inflammatory or obstructive bowel disease; myasthenia gravis; hypothyroidism; adreno-cortical insufficiency; respiratory depression; prostatic hyperplasia; pregnancy (Appendix 7c).

Adverse Effects Same as other opioids, however it has less addictive potential.

6. Antidiarrhoeals and Laxatives

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 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 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.

6.1 Antidiarrhoeal Symptomatic Drugs in Adult

Codeine* (Refer Page No. 10)

Pregnancy Category-C

Schedule H

Indications *Short-term symptomatic relief of acute diarrhoea in adult; pain.*

Availability **TABLET** 30 mg.

Dose ***Oral***

Adult- Symptomatic relief of acute diarrhoea: 30 mg 3 to 4 times daily.

Child- (1-12 years) 500 µg/kg 4-6 times daily.

Contraindications Conditions where inhibition of peristalsis should be avoided; abdominal distension; acute diarrhoeal conditions such as ulcerative colitis or antibiotic-associated colitis; acute respiratory depression.

Precautions Tolerance or dependence may occur with prolonged use; elderly and debilitated patients; hepatic impairment (Appendix 7a); renal impairment; lactation; overdosage: see chapter 7.2; interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting, constipation, drowsiness; respiratory depression and hypotension (large doses); dependence; difficulty with micturition; ureteric or biliary spasm; dry mouth, sweating, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, hypothermia, hallucinations, dysphoria, mood changes, miosis, decreased *libido* or potency, rash, urticaria, pruritus; convulsions (large doses).

Furazolidone

Pregnancy Category-C

Schedule H

Indications *Giardiasis; cholera; gastrointestinal infections; protozoal or bacterial diarrhoea and enteritis; food poisoning.*

Availability **TABLETS** 100 mg; **CAPSULE** 100 mg; **SUSPENSION** 25 mg/5 ml.

Dose ***Oral***

Adult- 100 mg 3 to 4 times a day.

Child- 5 mg/kg body weight daily in 4 divided doses.

Contraindications Hypersensitivity; alcoholics; primaquine sensitivity.

Precautions Urine colour changes to yellow after administration; orthostatic hypotension; hypoglycaemia; pregnancy (Appendix 7c); interactions (Appendix 6a, 6c).

Adverse Effects Nausea, vomitting, headache; hypotension; urticaria; dyspnea; dizziness.

Storage Store protected from light at temperature not exceeding 30°C.

Loperamide

Pregnancy Category-C

Schedule H

Indications *For the control and symptomatic relief of acute nonspecific diarrhoea and chronic diarrhoea associated with inflammatory bowel disease or gastroenteritis; for reducing the volume of discharge from ileostomies.*

Availability **TABLET/CAPSULE** 2 mg; **LIQUID** 1 mg/5 ml.

Dose ***Oral***

Adult- 4 mg initially thereafter 2 mg after every motion.

Child- 2 mg followed by 2 mg after every motion.

Contraindications Conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as active ulcerative colitis or antibiotic-associated colitis.

Precautions Liver disease; pregnancy: (Appendix 7c); interactions (Appendix 6c); glaucoma; Crohn's disease; urinary bladder obstruction.

Adverse Effects Abdominal cramps, dizziness, drowsiness and skin reactions including urticaria; paralytic ileus and abdominal bloating also reported; constipation; headache; meteorism; nausea; dry mouth; urinary retention.

Storage Store protected from light and moisture.

6.2 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 atonic 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 anthelminthic 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*

Pregnancy Category-B

Indications *Constipation.*

Availability **TABLETS** 5 mg; **SUPPOSITORIES** 5 and 10 mg.

Dose ***Oral/Rectal***

Adult and child over 10 years- 5 to 10 mg daily at night. Before radiological procedure and surgery: 16 to 20 mg at night before procedure.

Contraindications Intestinal obstruction (causes abdominal cramps), acute surgical abdominal conditions, acute inflammatory bowel disease, severe dehydration; faecal impaction, chronic use.

Precautions Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia; however, prolonged use may be justifiable in some circumstances; don't give antacid within 1 hour, pregnancy (Appendix 7c), inflammatory bowel disease, pre-existing heart disease or bowel disease, allergies, interactions (Appendix 6d).

Adverse Effects Tablets- griping; suppositories-local irritation; fainting, dizziness, soreness in anal region due to suppository leakage; abdominal discomfort, electrolyte imbalance, hypokalaemia.

Ispaghula*

Indications *Constipation; irritable colon syndrome.*

Availability **GRANULES** (flavoured and sweetened) 37.5 and 100g.

Dose ***Oral***

Adult- 6 teaspoonful of water or milk at night before bed time.

Child- 1-3 teaspoonful in water or milk before bed time.

Contraindications Intestinal obstruction; colonic atony; difficulty in swallowing.

Precautions Salt restriction; interactions (Appendix 6c).

Adverse Effects	Abdominal discomfort, flatulence, gastrointestinal obstruction.
Storage	Store protected from light and moisture.

Lactulose

Indications	*Constipation, hepatic encephalopathy.*
Availability	**SOLUTION/SYRUP** 3.35g/5 ml.
Dose	10 to 20g (15 to 20 ml/day, max 45 ml/day).
Contraindications	Galactosemia, intestinal obstruction, patients on low galactose diet.
Precautions	Lactose intolerance, diabetes mellitus.
Adverse effects	Diarrhoea (dose related), nausea, vomiting, hypokalaemia; dehydration; hypernatremia; bloating and abdominal cramps.

Senna

Pregnancy Category-C

Indications	*Constipation.*
Availability	**TABLETS** (containing Sennoside B-11.5 mg).
Dose	***Oral*** **Adult-** 2 to 4 tablets, usually at night; initial dose should be low, then gradually increased. **Child-** over 6 years, half the adult dose in the morning (on doctor's advice).
Contraindications	Intestinal obstruction; undiagnosed abdominal symptoms.
Precautions	Avoid prolonged use unless indicated for prevention of faecal impaction; pregnancy (Appendix 7c), lactation (Appendix 7b); hypersensitivity, undiagnosed abdominal pain, intestinal blockage.
Adverse Effects	Abdominal discomfort; atonic non-functioning colon and hypokalaemia (with prolonged use or overdosage); red or yellow brown urine, diarrhoea, nausea, vomiting, bloating.
Storage	Store protected from light and moisture.

6.3 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 the three 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 milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of lactation must be increased.

Plan B: Moderate dehydration: Whatever the child's age, a 4-h 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-h 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 min and then resumed at a slower rate (about one teaspoonful every 2 min). The child's status must be re-assessed after 4 h 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 h by mouth before infusion, then 5 ml/kg every h by mouth during intravenous rehydration). For intravenous supplementation, it is recommended that compound solution of sodium lactate (see chapter 28.2) is administered at a rate adapted to the child's age (infant under 12 months: 30 ml/kg over 1 h then 70 ml/kg over 5 h; child over 12 months:

the same amounts over 30 min and 2.5 h 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 h. If the child vomits, the rate of administration of the oral solution should be reduced.

Oral Rehydration Salts*

Indications *Dehydration from acute diarrhoea.*

Availability **GLUCOSE SALT SOLUTION** 5 and 37.5g.

Sodium chloride	2.6 g/litre of water
Sodium citrate	2.9 g/litre of water
Potassium chloride	1.5 g/litre of water
Glucose (anhydrous)	13.5 g/litre of water

When glucose and sodium citrate are not available, they may be replaced by

Sucrose (common sugar)	27 g/litre of water
Sodium bicarbonate	2.5 g/litre of water

In cases of cholera, oral rehydration salts containing a higher concentration of sodium may be required to prevent hyponatraemia.

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.

Dose ***Oral***

5g (single use): dissolve in water and drink; 37.5g: to reconstitute it with 1 litre of clean water.

Adult- Fluid and electrolyte loss in acute diarrhoea; 200 to 400 ml solution after every loose motion.

Precautions Renal impairment.

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.

Storage

Store protected from moisture in a sachet preferably made of aluminium foil containing sufficient powder for single dose or for a day treatment or for use in hospital.

7. Antidotes and Substances Used in Poisoning 81

7. Antidotes and Substances Used in Poisoning

These notes are only guidelines and it is strongly recommended that poisons information centres (Appendix 5) be consulted in cases where there is doubt about the degree of risk or about appropriate management.

7.1 Non specific

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 hour 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. Alkalinization 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 h 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 hour 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

Indications *Treatment of acute poisoning.*

Availability **POWDER** (for oral suspension), **TABLETS** 500 mg.

Dose ***Oral***

Adult and child over 12years- 50g, 0.5g/kg may be repeated every 4-6 h for upto 12-24 h.

Child- Below 12years; 1g/kg (max 50g). May be repeated every 4 h.

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, DDT), cyanides, malathion and metal salts including iron and lithium.

Adverse Effects Black stools; vomiting, constipation or diarrhoea; pneumonitis-due to aspiration.

Storage Store protected from moisture.

Calcium Disodium Edetate

Pregnancy Category-B

Indications *Lead poisoning (acute and chronic) and lead encephalopathy.*

Availability **AMPOULE** 5 ml (200 mg/ml).

Dose ***Intravenous injection***

Lead poisoning without encephalopathy: 1000 mg/m^2/day as continous infusion for 5 days.
Lead encephalopathy: 1500 mg/m^2/day by continous intravenous infusion in 5% dextrose or 0.9% NaCl (Final Concentration of edentate < 500 mg/100 ml), starting 4 h after first dose of BAL and after an adequate urine flow is established. Infusion is continued for 5 days.

Intramuscular injection *to be used if fluid overload is a concern.*

1000 mg/m^2/day divided into equal doses spaced 8 to 12 h apart.

Lignocaine or procaine should be added to the injection to minimize pain at the injection site.

Contraindications Anuria; patients with active renal disease or hepatitis; pregnancy (Appendix 7c).

Precautions Ensure adequate urine output, pre-existing mild renal disease; patients with lead encephalopathy and cerebral edema may experience a lethal increase in intracranial pressure following intravenous infusion, the intramuscular route is preferred for these patients.

Adverse Effects Renal tubular toxicity which may lead to acute renal failure, fever, chills, lacrimation, increased prothrombin time, pain at intramuscular injection site; hypotension; cardiac rhythm irregularities; thirst; headache; fatigue; malaise; urinary frequency; glycosuria; proteinuria; microscopic hematuria; histamine-like reactions.

7.2 Specific

Paracetamol Overdosage:

Paracetamol in a dose of 10-15g or 150 mg/kg of paracetamol taken within 24 h may cause severe hepatocellular necrosis and less frequently renal tubular necrosis. The only early features of poisoning, nausea and vomiting, usually settle within 24 h. Persistence beyond this time, often with the onset of right subcostal 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 12g, whichever is smaller, is thought to have been ingested within the previous hour.

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

In remote areas methionine should be given, since administration of acetylcysteine outside hospital is not generally practicable. Once the patient is in hospital the need to continue antidote treatment can be assessed from plasma-paracetamol concentrations.

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.

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 ingestion, 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).

Iron Poisoning and Iron and Aluminium Overload:

Mortality from iron poisoning is reduced by specific therapy with desferrioxamine which chelates iron. Before administration of desferrioxamine the stomach should be emptied by gastric lavage (with a wide-bore tube) within 1 h of ingesting a significant quantity of iron or if radiography reveals tablets in the stomach. Desferrioxamine 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.

Heavy Metal Poisoning:

Heavy metal poisoning may be treated with a range of antidotes including dimercaprol, penicillamine, potassium ferric hexacyanoferrate and Sodium calcium edetate. Penicillamine is also used to promote excretion of copper in Wilson's disease.

Methaemoglobinaemia:

Methylthioninium chloride can lower the levels of methaemoglobin in red blood cells and is used in the treatment of methaemoglobinaemia. In large doses, it may cause methaemoglobinaemia and therefore methaemoglobin levels should be monitored during treatment.

Cyanide Poisoning:

Cyanide poisoning may be treated with Sodium nitrite followed by Sodium thiosulphate.

Atropine* (Refer Page No. 419 and 560)

Pregnancy Category-C

Schedule H

Indications — *Organophosphate and carbamate poisoning; premedication; antispasmodic; as mydriatic; cycloplegic refraction procedures.*

Availability — **INJECTION** 1 ml ampoules and 50 ml vial (0.6 mg/ml).

Dose — ***Intramuscular and intravenous injection***

Adult- 1.8 - 3.0 mg intravenous bolus followed by doubling dose every 3 to 5 minutes depending upon response. End-point for atropinization include clear chest with no wheeze, systolic BP >80mm Hg, pulse >80 beats/min., pupils no longer pinpoint and dry axillae. Following that infusion of atropine at 10-20 % of total initial dose required/hour; may require boluses during infusion.

Child-20-30 µg/kg initially with same schedule as above.

Contraindications — In myasthenia gravis (but may be used to decrease muscarinic side-effects of anticholinesterases), paralytic ileus, pyloric stenosis and prostatic enlargement; reflux oesophagitis; unstable cardiac rhythm.

Precautions — Elderly, Down syndrome; angle-closure glaucoma; myasthenia gravis; prostatic enlargement; pyrexia; lactation (Appendix 7b); interactions (Appendix 6a); pregnancy (Appendix 7c).

Adverse Effects — Constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin. Occasionally, confusion (particularly in the elderly), nausea, vomiting and giddiness; very rarely, angle-closure glaucoma may occur.

Desferrioxamine Mesylate*

Pregnancy Category-C

Indications — *Acute iron poisoning; chronic iron overload; aluminium overload; primary hemochromatosis.*

Availability — **INJECTION** 5 ml and 10 ml vial (500 mg/vial).

Dose — ***Continuous intravenous infusion***

Adult and Child- Begin with 5 mg/kg/h, increasing over 15 minutes if tolerated to 15 mg/kg/h, to minimize the risk of hypotension. After 1 to 2 h reduce to 3-4 mg/kg/h for the next 22-23 hrs (max dose is 100 mg/kg over 24 hrs).

Patients with cardiovascular collapse: 5 mg/kg/h (up to max. of 80 mg/kg in 24 h.)

Chronic iron overload: Intramuscular 500 to 1000 mg daily, in addition 2g by intravenous infusion with each unit of blood transfused.

Contraindications Severe renal disease; pregnancy (Appendix 7c).

Precautions Renal impairment; eye and ear examinations before and at 3-month intervals during treatment; aluminium encephalopathy (may exacerbate neurological dysfunction); children under 3 years (may retard growth); lactation; interactions (Appendix 6c).

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, acute respiratory distress syndrome; pain on intramuscular or subcutaneous injection; local irritation on prolonged subcutaneous infusion; reddish-brown discolouration of urine.

Storage Store protected from light in refrigerator (2-8^{o}C). Do not freeze.

Dimercaprol (BAL)*

Pregnancy Category-C

Indications *Acute poisoning by antimony, arsenic, bismuth, copper gold, mercury and possibly thallium; adjunct (with sodium calcium edetate) in lead poisoning.*

Availability **OILY INJECTION** 2 ml ampoule (50 mg/ml).

Dose ***Intramuscular injection***

To be administerd by deep intramuscular injection only
Lead poisoning: Adults-4 mg/kg every 4 h for 5 days. Child- 75 mg/m^2 every 5 h for 5 days. Arsenic poisoning: 3 mg/kg every 4 h for 48 h and then twice a day for 7-10 days. Mercury poisoning: 5 mg/kg followed by 2.5 mg/kg every 12-24 h for upto 10 days

Contraindications Not indicated for iron, selenium or cadmium poisoning; severe hepatic impairment (unless due to arsenic poisoning); hypertension; tellurium poisoning, peanut allergy, G-6-PD deficiency.

Precautions Hypertension; renal impairment (discontinue or use with extreme caution if renal failure occurs during treatment); any abnormal reaction such as hyperpyrexia should be assessed; elderly; pregnancy (Appendix 7c); lactation, alkalinize urine to pH of 7.5-8.0 using sodium bicarbonate.

Adverse Effects Hypertension, tachycardia; malaise, nausea, vomiting, abdominal pain, salivation, lacrimation, sweating, burning sensation in the mouth, throat and eyes; feeling of constriction in throat and chest; headache, muscle spasms, tingling of the extremities; fever in children; local pain and abscess at injection site, iron toxicity potentiation.

Storage Store protected from light.

D-Penicillamine* (Refer Page No. 385)

Pregnancy Category-D

Schedule H

Indications *Poisoning by heavy metals, particularly lead and copper; Wilson's disease; severe rheumatoid arthritis.*

Availability **CAPSULE/TABLET** 250 mg.

Dose ***Oral (given before food)***

Adult- 1 to 2g daily in three divided doses starting with 250 mg OD and gradually increasing to full dose over 2-3 weeks.

Child- 20 mg/kg/day administered in 3-4 divided doses, initiating treatment at 25% of this dose and gradually increasing to full dose over 2-3 weeks to minimize adverse reactions. Continue till blood lead levels <45 µg/dl.

Contraindications Hypersensitivity; lupus erythematosus; gold or antimalarial drug; penicillamine-induced agranulocytosis; aplastic anaemia; thrombocytopenia, pregnancy, lactation (for rheumatoid arthritis).

Precautions Monitor throughout treatment including blood counts and urine tests; renal impairment; immunosuppressive treatment; avoid oral iron within 2 h of a dose; hepatic impairment; pregnancy (Appendix 7c).

In Wilson's disease, consider withdrawal if platelet count falls below 120 000/mm^3 or white blood cells below 2500/mm^3 or if 3 successive falls within reference range (can restart at reduced dose when counts return to reference range but permanent withdrawal necessary if neutropenia or thrombocytopenia recur).

In Wilson's disease warn patient to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers or rashes develop.

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).

Flumazenil*

Pregnancy Category-C

Indications *Antidote for benzodiazepine overdose, reversal of sedative effects produced by benzodiazepenes administered during general anaesthesia or diagnostic or therapeutic procedures.*

Availability **INJECTION** 0.1 mg/ml.

Dose

Adult- 0.2 mg (2 ml) administered over 30 seconds, i.v, repeat 0.3 mg and 0.5 mg at 1-2 minute intervals. Not more than 3 mg over one hour.

Child- 10 µg/kg, i.v, for 2 doses.

Contraindications

Epilepsy, neuromuscular blockade, hypersensitivity to benzodiazepines, patients of suspected tricyclic antidepressant overdose, raised intracranial pressure.

Precautions

History of seizures, panic attack, alcohol drug dependence, bleeding disorder, liver disease, head injury, respiratory depression, pregnancy (Appendix 7c).

Adverse effects

Convulsions, fatigue, injection site pains, increased sweating, facial erythema, raised intracranial pressure, agitation, dizziness, abnormal vision, may cause complete heart block, flushing, transient increase in blood pressure and heart-rate.

Methylene Blue (Methylthioninium Chloride)*

Pregnancy Category-C

Indications

Acute methaemoglobinaemia.

Availability

INJECTION 10 mg/ml.

Dose

Intravenous injection

Methaemoglobinaemia caused by high dosage of prilocaine infusion: 1-2 mg/kg intravenously over 5 minutes, followed immediately by a fluid flush of 15-30 ml to minimize local pain. May be repeated in 30-60 minutes. Maximum dose: 7 mg/kg.

Contraindications

Severe renal impairment; methaemoglobinaemia due to chlorate or induced by sodium nitrite in treatment of cyanide poisoning; affects ability to drive machinery.

Precautions

G-6-PD deficiency-may cause haemolytic anaemia; monitor blood methaemoglobin throughout treatment; pregnancy (Appendix 7c); lactation.

Adverse Effects

Nausea, vomiting, abdominal pain, chest pain, headache, dizziness, confusion, profuse sweating; hypertension or hypotension reported; haemolytic anaemia-in G-6-PD deficiency; methaemoglobinaemia-with high dosage; bluish skin discolouration; blue saliva, urine and faeces.

Storage Store protected from light in an airtight container.

Naloxone*

Pregnancy Category-B

Schedule X

Indications *Opioid overdosage; postoperative respiratory depression.*

Availability **INJECTION** 0.4 mg/ml.

Dose ***Intravenous injection***

Subcutaneous or intramuscular route (if i.v. route is not feasible but the dose is same, can be given oral as well).

Adult- Opioid poisoning: Start with 0.4 to 2 mg (at all ages) as intravenous bolus, Repeat every 2 minutes if no response to a total of 10 mg. Once response occurs start infusion of naloxone at 2/3rd the total loading dose given every hour with continous monitoring for reccurence of respiratory depression. May require additional bolus during infusion.

Child- Opioid poisoning: 10 µg/kg, followed by 100 µg/kg if there is no response.

Contraindications Hypersensitivity.

Precautions Physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated (see above); lactation; cardiovascular disease; pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting, sweating-may also be due to opioid withdrawal.

Storage Store protected from light in an airtight container.

Pralidoxime (2-PAM)*

Pregnancy Category-C

Schedule H

Indications *Adjunct to atropine in the treatment of organophosphate poisoning and anticholinesterase overdosage used in the treatment of myasthenia gravis (mg), respiratory depression or severe muscle weakness due to carbamate poisoning.*

Availability

INJECTION i.v infusion 500 mg/20 ml, 1g/20 ml (as chloride and iodide salt).

Dose

For Chloride salt, 30 mg/kg i.v. over 15-20 minutes followed by infusion at 8-10 mg/kg/h. To be continued 12-24 hours after atropine is no longer required.
For Iodide salt, dose is about 30% higher than chloride salt.

Child- 25 to 50 mg/kg, diluted to 5% concentration in NS and infused over 5-30 minutes. May be repeated after one h, then every 6 to 12 h.

Severe poisoning:
Adult- 500 mg/h via continuous infusion. max.- 12g/24 h.

Child- 9 to 19 mg/kg/h.

For anticholinesterase overdose in MG:
Adult- 1-2g i.v. initially, then 250 mg every 5 minutes.

Child (0-18 years)- 15-25 mg/kg by slow i.v (up to 1 g).

Maintainance dose- (< 12 years) 15-50 mg/kg i.v every 5 minutes (up to 250 mg).

Contraindications

Carbamate poisoning and organophosphates without anticholinesterase activity; hypersensitivity to the drug.

Precautions

Impaired renal function; large doses can cause neuromuscular blockade, myasthenia gravis; atropinization occur faster on concurrent use with atropine; paediatrics; allergies; pregnancy (Appendix 7c).

Adverse effects

Headache, nausea; blurred vision, drowsiness, dizziness, impaired accommodation, tachycardia, hyperventilation, muscular weakness; transient elevation in SGOT and/or SGPT levels; laryngospasm and rigidity.

Storage

Store protected from moisture.

Sodium Nitrite*

Pregnancy Category-C

Indications

Cyanide poisoning (together with Sodium thiosulphate).

Availability **INJECTION** 30 mg/ml (10 ml).

Dose ***Intravenous injection (over 5 to 20 min)***

Adult-300 mg at 2.5-5.0 mg/minute.

Child- 4 to 10 mg/kg (max 300 mg) at 5 mg/minute.

Note: Prepare as 3% solution of Sodium nitrite in Water for Injections (30 mg/ml) at the time of administration.

Contraindications Methaemoglobinaemia; hemolytic anaemia; G-6-PD deficiency.

Precautions Monitor plasma methaemoglobin levels; severe cardiovascular or cerebrovascular disease; hypotension; pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting and abdominal pain, vasodilatation resulting in syncope, hypotension, tachycardia, flushing, headache; methaemoglobinaemia; cyanosis, dyspnoea, tachypnoea.

Sodium Thiosulphate* (Refer Page No. 352)

Pregnancy Category-C

Indications *Prophylactically with prolonged use of nitro prusside to prevent cyanide toxicity, cyanide poisoning (together with Sodium nitrite); pityriasis versicolor; skin disease.*

Availability **INJECTION** 250 mg/ml; 500 mg/ml (50 ml).

Dose ***Intravenous injection (over 10 min).***

Adult- 12.5g intravenously over 10-30 minutes may be repeated at half the initial dose at 1-2 hours.

Child- 500 mg/kg intravenously over 10-30 minutes may be repeated at half the initial dose at 1-2 hours (12.5g maximum)

Contraindications Hypersensitivity; pregnancy (Appendix 7c).

Adverse Effects Irritation; urticaria; hypotension; burning; stinging on application.

Note: Freshly prepare by dissolving Sodium thiosulphate IP in Water for Injections.

8. Antiemetics

Antiemetics are drugs effective against nausea and vomiting. They are typically used to treat motion sickness and the side effects of opioid analgesics, general anaesthetics and chemotherapy induced nausea and vomiting in cancer patients either alone or in combination.

They act on the brain by preventing the stimulation of the vomiting centre (chemoreceptor trigger zone-CTZ). Some medications act on the gut by speeding up the rate at which the stomach empties and help to facilitate the quick transit of food through intestine (prokinetic action).

Classification:

- 5-HT_3 receptor antagonists block serotonin receptors in the central nervous system and gastrointestinal tract: Ondansetron, Granisetron, Dolasetron etc.
- Dopamine D_2-receptor antagonists act in the brain: Domperidone, Metoclopramide, Mosapride etc.
- Antihistamines or H_1- histamine receptor antagonists: Diphenhydramine, Promethazine etc.
- Benzodiazepines: Midazolam, Lorazepam etc.
- Anticholinergics: Scopolamine, Hyoscine, Dicyclomine etc.
- Steroids: Dexamethasone etc.

Metoclopramide has antiemetic properties and also stimulates upper gastrointestinal motility. It 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. It 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 crisis. 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 h of drug withdrawal.

Promethazine is a phenothiazine derivative. In addition to D_2

dopaminergic blockade it has pronounced histamine H_1 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.

Domperidone*

Schedule H

Indications — *Nausea and vomiting from any cause in adult, epigastric senses of fullness; upper abdominal distress; non ulcer dyspepsia; migraine.*

Availability — **TABLETS** 5 and 10 mg; **SYRUP** 30 ml (1 mg/ml); **CAPSULE** 30 mg.

Dose — ***Oral***

Adult- 10 to 20 mg 3 to 4 times a day
Child- 0.3 to 0.6 mg/kg TDS.

Contraindications — Hypersensitivity; prolactinoma, hepatic impairment; where increased gastro-intestinal motility harmful; pregnancy; gastro intestinal haemorrhage; intestinal obstruction.

Precautions — Children; renal impairment, interactions (Appendix 6c); history of breast cancer; allergies; pheochromocytoma; i.v. administration can lead to hypokalaemia and cardiac arrhythmias.

Adverse Effects — Rarely, gastro-intestinal disturbances (including cramps) and hyperprolactinaemia; very rarely, extrapyramidal effects and rashes; headache; dizziness; dry mouth; nervousness; flushing.

Storage — Store protected from light and moisture.

Metoclopramide* (Refer Page No. 421)

Pregnancy Category-B

Schedule H

Indications — *Nausea and vomiting in gastrointestinal disorders and treatment with cytotoxics or radiotherapy; gastro-oesophageal reflux disease; gastroparesis; premedication and postoperatively; aid to gastrointestinal intubation; nausea and vomiting in migraine; diabetic gastric stasis.*

Availability

TABLETS 10 and 15 mg; **INJECTION** 2 ml ampoule (5 mg/ml); **SYRUP** 30 ml (1 mg/ml).

Dose

Oral or intramuscular injection or Slow intravenous injection

Adult- Nausea and vomiting, gastro-esophageal reflux, gastroparesis: (over 1 to 2 min for slow intravenous injection), 10 mg 3 times daily. 15 to 19 years (under 60 kg) 5 mg 3 times daily. Aid to gastrointestinal intubation: 20 mg as a single dose 5 to 10 min before examination; Adolescent (15 to 19 years), 10 mg.

Child- Up to 1 year (up to 10 kg) 1 mg twice daily; 1 to 3years (10 to 14 kg) 1 mg 2 to 3 times daily; 3 to 5 years (15 to 19 kg) 2 mg 2 to3 times daily; 5 to 9 years (20 to 29 kg) 2.5 mg 3 times daily; 9 to 14 years (30 kg and over) 5 mg 3 times daily (usual max. 500 µg/kg daily, particularly for children and young adult).

Slow intravenous injection only

Adult- Premedication: 10 mg as a single dose.

Contraindications

Gastrointestinal obstruction, haemorrhage or perforation, 3-4 days after gastrointestinal surgery; convulsive disorders; pheochromocytoma; hypersensitivity.

Precautions

Elderly, children and young adults; hepatic impairment (Appendix 7a); renal impairment (Appendix 7d); pregnancy (Appendix 7c); may mask underlying disorders such as cerebral irritation; avoid for 3-4 days after gastrointestinal surgery; lactation (Appendix 7b); interactions (Appendix 6a); Parkinson's disease; epilepsy; depression; porphyria; driving or operating machines; hypertension; cirrhosis; congestive heart failure.

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, methaemoglobinaemia (more severe in G-6-PD deficiency); galactorrhoea; amenorrhoea; bradykinesia; gynaecomastia; insomnia.

Storage

Store protected from light and moisture.

Ondansetron*

Pregnancy Category-B

Schedule H

Indications

Postoperative nausea and vomiting, chemotherapy and/or radiotherapy induced nausea and vomiting.

Availability

TABLETS 4 and 8 mg; **INJECTION** 2 and 4 ml ampoule (2 mg/ml); **DROPS** 2 mg/5 ml; **SYRUP** 2 mg/5 ml; **SUSPENSION** 1 mg/5 ml.

Dose

Oral

Prevention of post-operative nausea and vomiting: Adult 16 mg, 1 h before induction of anaesthesia.

Nausea and vomiting associated with cancer chemotherapy:
Adult- 24 mg as a single dose taken 30 min before start of single day chemotherapy.

Child (4-11 yrs)- 4 mg tablets 3 times a day; continue for 1-2 days after completion of chemotherapy.

Parenteral

Post-operative nausea and vomiting:
Adult- 4 mg by i.m or slow i.v as a single dose.

Prevention of chemotherapy-induced nausea and vomiting:
Adult- single 32 mg i.v dose infused over 15 min begining 30 min before start of emetogenic chemotherapy.

Contraindications

Hypersensitivity.

Precautions

Moderate to severe liver impairment; pregnancy (Appendix 7c), lactation; hypersensitivity to other selective 5-HT_3 - receptor antagonists, subacute intestinal obstruction; cardiac disease, electrolyte abnormalities, QT interval prolongation (avoid concomitant administration of drugs that prolong QT interval), interactions (Appendix 6c).

Adverse Effects

Headache, constipation or diarrhoea, dizziness; flushing, hypersensitivity reaction, anaphylaxis/anaphylactoid reactions, angioedema; bronchospasm, hypotension, laryngeal edema, urticaria, hiccups, oculagyric crisis.

Prochlorperazine

Pregnancy Category-C

Schedule H

Indications *Nausea and vomiting.*

Availability **TABLETS** 3 and 5 mg; **INJECTION** 1 ml ampoule (2.5 mg/ml).

Dose ***Oral and intravenous injection***

Adult- Nausea, vomiting acute attack: initially 20 mg then 20 mg every 2 h. Prevention; 5 to 10 mg 2 to 3 times daily.

Child- (over 10 kg only).

Oral: 0.4 mg/kg/day in 3-4 divided doses.

Intravenous injection: 0.13 mg/kg/day in 3-4 divided doses.

Adult- Labyrinthine disorder: 5 mg 3 times daily increased to 30 mg daily in divided doses that decrease after meal to 5 to 10 mg daily.

Child- Labyrinthine disorder Not recommended.

Intravenous injection: 0.13 mg/kg/day in 3-4 divided doses.

Contraindications Comatose states, CNS depression and pheochromocytoma. Most antipsychotics are best avoided during pregnancy; hypersensitivity; prolactin dependant tumors.

Precautions Patients with hepatic impairment, renal impairment, cardiovascular disease, Parkinson's disease (may be exacerbated by antipsychotics), epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, prostatic hypertrophy, or a susceptibility to angle-closure glaucoma. Caution is also required in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops). Caution should be taken in elderly, who are particularly susceptible to postural hypotension and to hyper- or hypothermia in very hot or cold weather. Serious consideration should be given before prescribing these drugs for elderly patients. As photosensitisation may occur with higher dosages, patients should avoid direct sunlight; extrapyramidal syndrome; pregnancy (Appendix 7c); interactions (Appendix 6a).

Adverse Effects Less sedating; extrapyramidal symptoms, particularly dystonias, more frequent; respiratory depression may occur in susceptible patients; amenorrhoea; blurred vision; cholestatic jaundice; neuroleptic malignant syndrome; leucopenia; agranulocytosis.

Storage Store protected from light and moisture.

Promethazine* (Refer Page No. 423)

Pregnancy Category-C

Schedule G

Indications *Nausea, vomiting, labyrinthine disorders, motion sickness; premedication; allergic rhinitis; vasomotor rhinitis.*

Availability **TABLETS** 10 and 25 mg; **SYRUP** 60 ml (5 mg/5 ml); **INJECTION** 2 ml ampoule (25 mg/ml).

Dose ***Oral***

Nausea and vomiting (including postoperative): 12.5 to 25 mg, repeated at intervals of not less than 4 h (usual max., 100 mg in 24 h). Motion sickness, prevention: 20 to 25 mg at bedtime on night before travel, repeated on day of travel if necessary.

Child- Motion sickness, prevention; 2 to 5 years: 5 mg at night and on day of travel, if necessary. 5 to 10 years: 10 mg at night and on day of travel, if necessary.

Intramuscular injection or Slow intravenous injection

Nausea and vomiting (including postoperative); (diluted to 2.5 mg/ml in water for injection); 12.5 to 25 mg, repeated at intervals of not less than 4 h (usual max., 100 mg in 24 h).

Contraindications

Porphyria; hypersensitivity; coma; hypokalaemia.

Precautions

Prostatic hypertrophy; urinary retention; glaucoma; hepatic disease (Appendix 7a); epilepsy; elderly and children (more susceptible to adverse effects); lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6a).

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

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; somnolence; torticollis; tinnitus; leucopenia; thrombocytopenia, agranulcytosis; apnoea; angioneurotic edema.

Storage

Store protected from light and moisture.

9. Anti-Infectives 105

9. Anti-Infectives

9.1 Antiamoebic, Antigiardiasis and Antitrichomoniasis 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, sympto mless carriers should be treated with a luminal amoebicide which will reduce the risk of transmission and protect the patient from invasive amoebiasis. Diloxanide furoate is most widely used, but other compounds, including clefamide, etofamide and teclozan, are also effective. Treatment with diloxanide furoate is regarded as successful if stools are free of *E. histolytic*a for one month. Several specimens should be examined in evaluating response to treatment.

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 sympto mless 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.

Diloxanide Furoate*

Schedule H

Indications	*Amoebiasis (asymptomatic carriers in non-endemic areas; eradication of residual luminal amoebae after treatment of invasive disease with other drugs).*
Availability	**TABLET** 500 mg.
Dose	***Oral***
	Adult- 500 mg every 8 h for 10 days.
	Child- 20 mg/kg body weight daily in three divided doses for 10 days.
Contraindications	Lactation (Appendix 7b); systemic amoebiasis.
Precautions	Pregnancy (defer treatment until after first trimester).
Adverse Effects	Flatulence; occasionally vomiting, pruritus and urticaria; furred tongue.
Storage	Store protected from light.

Metronidazole* (Refer Page No. 140)

Pregnancy Category-B

Schedule H

Indications	*Invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections; bacterial infections; Helicobacter pylori eradication; ulcerative gingivitis.*

Availability — **TABLETS** 200 and 400 mg; **SUSPENSION** 200 mg/5 ml; **INJECTION** 500 mg in 100 ml infusion.

Dose

Oral

Adult- Amoebiasis: 400 to 800 mg three times a day for 5 to7 days. **Giardiasis:** 200 mg three times a day for 7 to 10 days.

Child- 35 to 50 mg/kg body weight in amoebiasis and 10 to 15 mg/kg body weight in giardiasis.

Intravenous injection

Adult- 500 mg every eight h up to 7 days.

Child- (Below 12 years) 7.5 mg/kg body weight.

Contraindications — Chronic alcohol dependence; neurological disease, blood dyscrasias, first trimester of pregnancy.

Precautions — Disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 7a); pregnancy (Appendix 7c); see also notes above); lactation (Appendix 7b); clinical and laboratory monitoring in courses lasting longer than 10 days; interactions (Appendix 6a, 6c, 6d); prolonged use may result in fungal or bacterial superinfection, phenobarbitones, history of seizure disorder.

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; anorexia, glossitis, dryness of mouth.

Storage — Store protected from light and moisture. Store injection in a single dose container.

Tinidazole

Pregnancy Category-C

Schedule H

Indications — *Amoebiasis, trichomoniasis and giardiasis, anaerobic infections, necrotising ulcerative gingivitis, bacterial vaginosis, H. pylori associated peptic ulcers, abdominal surgery prophylaxis.*

Availability

TABLETS 300 and 500 mg, 1g; **INJECTION** 400 ml infusion (2 mg/ml); **SUSPENSION** 75 mg/5 ml, 150 mg/5 ml.

Dose

Oral

Anaerobic infections:
Adult- 2g on first day, followed by 1g daily or 0.5g twice daily for 5-6 days.

Amoebiasis:
Adult- 1.5 - 2g daily as a single dose for 3 - 6 days.

Child- 30-50 mg/kg daily as a single dose for 3 days.

Trichomoniasis and giardiasis:
Adult- 2g as a single dose.

Child- 50 to 75 mg/kg as a single dose.

Parenteral

Bacterial vaginosis and ulcerative gingivitis:
Adult- 2g as a single dose parenterally.

Anaerobic infections:
Adult- Initially 800 mg/400 ml infused i.v. at a rate of 10 ml/minute followed by 800 mg daily.

Abdominal surgical prophylaxis:
Adult- 2.0g as single i.v. infusion 12 h prior to surgery.

Contraindications

Hypersensitivity to nitroimidazole derivatives, first trimester of pregnancy (Appendix 7c), lactation, blood dyscrasias, porphyria; interactions (Appendix 6a).

Precautions

Seizures, peripheral neuropathy, CNS disease, disulfiram-like reaction with alcohol.

Adverse effects

Similar to metronidazole.

Storage

Store protected from light and moisture.

9.2 Antibacterial Drugs

Beta-Lactams:

Beta-lactam antibiotics including penicillins, cephalosporins and carbapenems share a common structure; they are bactericidal, their mechanism of action resulting from inhibition of peptidoglycan, a mucopeptide in bacterial cell walls. Benzylpenicillin and phenoxymethylpenicillin 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.

Cephalosporins 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 cephalosporin 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 penicillinases. 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 penicllin administration are at risk of immediate hypersensitivity to penicillin. These individuals should not receive penicillin, rather a cephalosporins or another beta-lactam antibiotic may be used. 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 cephalosporins 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 h 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.

Ampicillin, Amoxycillin, Amoxycillin 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 1g every 6 h for 7-10 days.

Amoxycillin 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. Amoxycillin 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 Amoxycillin widens Amoxycillin's spectrum of activity and allows its use against Amoxycillin-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.

Benzylpenicillin and Phenoxymethylpenicillin:

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 h. Benzathine benzylpenicillin or procaine benzylpenicillin provides a tissue depot from which the drug is slowly absorbed over a period of 12 hour to several days. They are the preferred choice for the treatment of syphilis or yaws.

Phenoxymethylpenicillin 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.

Cephalosporins and Imipenem with Cilastatin:

Ceftazidime and **ceftriaxone** are third generation cefalosporins. 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. Ceftazidime is active against *Pseudomonas aeruginosa* and other Gram-negative bacteria; it is used in the treatment of pseudomonal 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 *P. aeruginosa*, which are resistant to other more usual treatments.

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.

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.

Aminoglycosides:

Aminoglycosides including **gentamicin** 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 concen-

tration 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.

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.

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 persistance 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.

Metronidazole:

Metronidazole has high activity against anaerobic bacteria and protozoa. Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible.

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.

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. Trimethoprim is also used alone for respiratory-tract infections and, in particular, for urinary-tract infections.

Vancomycin:

Vancomycin is not significantly absorbed from the gastrointestinal tract and must be given intravenously for systemic infections which cannot be treated with other effective, less toxic antimicrobials. It is used to treat serious infections due to Gram-positive cocci including methicillin-resistant staphylococcal infections, brain abscess, staphylococcal meningitis and septicaemia.

Amoxycillin*

Pregnancy Category-B

Schedule H

Indications	*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.*
Availability:	**TABLETS** 250 mg, 500 mg; **KID TABLETS** 125, 250 mg; **CAPSULES** 250, 500 mg; **DRY SYRUP** 125 and 250 mg per 5 ml; **INJECTION** 1 ml ampoule (100 mg/ml), 250 mg/vial; **DROP** 10 ml (100 mg/ml).
Dose	***Oral***
	Adult- 250 mg every 8 h, double in severe infection.

Otitis media: 1g every 8 h.

Enteric fever: 2 to 4g daily in divided doses for 14 to 21 days.

Intramuscular injection

500 mg every 8 h.

Intravenous injection or infusion

500 mg every 8 h, increase to 1g every 6 h in case of severe infection.

Child up to 10 years- 125 mg every 8 h, double in severe infections.

Otitis media: 40 mg/kg body weight daily in three divided doses.

Enteric fever: 50 to 100 mg/kg body weight in three divided doses for 14 to 21 days.

Intramuscular injection

50 to 100 mg/kg body weight in divided doses.

Intravenous injection or infusion

50 to 100 mg/kg body weight in divided doses.

Contraindications

Hypersensitivity to penicillins (see notes above).

Precautions

History of allergy; renal impairment; erythematous rashes common in glandular fever, chronic lymphatic leukaemia and possibly HIV infection; lactation (Appendix 7b); interactions (Appendix 6b, 6c, 6d); possibility of super infection with mycotic pathogens, mononucleosis, hepatic impairment (Appendix 7a); pregnancy (Appendix 7c).

Adverse Effects

Nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response, may be serious reaction-discontinue treatment); hypersensitivity reactions including Steven's Johnson syndrome, urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis; rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; rarely, central nervous system disorders including convulsions associated with high doses or impaired renal function; mucocutaneous candidiasis, with discolouration; agitation.

Storage

Tablet, Capsule and Oral suspension: Store protected from moisture at a temperature not exceeding 30°C. Injection: Store protected from moisture in a sterile, tamper evident container sealed so as to exclude micro-organisms at temperature not exceeding 30°C.

Amoxycillin + Clavulanic acid*

Pregnancy Category-B

Schedule H

Indications

Treatment of infections caused by susceptible organisms, sinusitis, otitis media, dental abcesses, severe respiratory tract infections, urinary tract infections, skin and soft tissue infections, surgical prophylaxis.

Availability

TABLETS

Amoxycillin	+	Clavulanic acid
500 mg	+	125 mg
250 mg	+	125 mg
875 mg	+	125 mg
200 mg	+	28.5 mg (DT)

CAPSULS

Amoxycillin	+	Clavulanic acid
500 mg	+	125 mg
250 mg	+	125 mg

SUSPENSION

Amoxycillin	+	Clavulanic acid
200 mg	+	28.5 mg/5 ml
125 mg	+	31.25 mg/5 ml
250 mg	+	62.5 mg/5 ml

INJECTION

Amoxycillin	+	Clavulanic acid
250 mg	+	50 mg
1g	+	200 mg
125 mg	+	25 mg
500 mg	+	100 mg

Dose

Oral

Upper and lower respiratory tract infections, sinusitis, otitis media, skin and soft tissue infections, susceptible infections:
Adult- 250-500 mg every 8 hours or 500-750 mg every 12 hours.

Child- 125-250 mg every 8 hours;
Children weighing <40 kg: 20-40 mg/kg/day in divided doses every 8 hours;
Infants <3 months: up to 30 mg/kg/day in divided doses every 12 hours.

Dental abcesses: Adult- 3 g as a single dose, followed by a second dose 8 hours later.

Severe or recurrent respiratory tract infections: Adult-3 g twice daily.
Child (2-6 years)- 5 ml twice daily;
(7-12 years)- 10 ml twice daily before meals, upto 14 days (dose should be specified in terms of strength).

Parenteral

Susceptible infections and surgical prophylaxis: Adult- 500 mg every 8 hr. In severe infections, dose may be increased to 1 g every 6 hours, upto 14 days. Can be given via i.m or slow i.v over 3-4 minutes or i.v infusion over 30-60 minutes.
Child: <10 years: 50-100 mg/kg/day in divided doses.

Contraindications Hypersensitivity to penicillins, infectious mononucleosis, jaundice.

Precautions Renal impairment, hepatic dysfunction, patients on anticoagulant therapy, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).

Adverse Effects GI upset, mycosis, rash, nausea, vomiting, anaphylaxis, cholestatic jaundice, blood dyscracias, toxic epidermal necrolysis, convulsions, exfoliative dermatitis, Stevens Johnson syndrome, angioedema, hepatitis, tooth discolouration.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Ampicillin*

Pregnancy Category-B

Schedule H

Indications *Mastoiditis; gynaecological infections; septicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis; respiratory tract infection.*

Availability **TABLETS** 125 and 250 mg; **CAPSULES** 250, 500 mg and 1g; **DRY SYRUP** 125 and 250 mg/5 ml; **INJECTION** 100, 250 and 500 mg/vial.

Dose ***Oral***

Adult- 250 mg to 1g every 6 h at least 30 min before food.

Urinary tract infection Adult- 500 mg every 8 h.

Children under 10 years- Half of adult dose.

Intramuscular and intravenous injection or infusion

500 mg every 4 to 6 h.

Listeria meningitis (in combination with antibiotics); by intravenous infusion 2g every 4h for 10 to 14 days.

Child- Half of the adult dose.

Listeria meningitis (in combination with antibiotics); infants 1 to 3 months; 50 to 100 mg/kg body weight every 6 h. 3 months to 12 years; 100 mg/kg body weight every 76 h (max 12g daily).

Contraindications Hypersensitivity to penicillins (see notes above).

Precautions History of allergy (see notes above); renal impairment (Appendix 7d); erythematous rashes common in glandular fever, acute or chronic lymphocytic leukaemia and cytomegalovirus infection; lactation (Appendix 7b); interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).

Adverse Effects Nausea and vomiting, diarrhoea; rashes, high fever (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; sore tongue; asthma.

Storage **Tablets, Capsule, Oral suspension:** Store protected from moisture and light at a temperature not exceeding 30°C. Injection: Store protected from light in a sterile tamper evident container sealed so as to exclude micro-organisms at a temperature not exceeding 30°C.

Azithromycin*

Pregnancy Category-B

Schedule H

Indications *Uncomplicated genital chlamydial infections and trachoma.*

Availability **TABLETS** 100, 250 and 500 mg; **CAPSULES** 250 and 500 mg; **INJECTION** 500 mg/vial **DRY SYRUP** 100, 200 mg/5 ml.

Dose ***Oral***

Adult- 500 mg once daily for 3 days or 500 mg on first day then 250 mg once daily for 4 days.

Child- over 6 months: 10 mg/kg body weight once daily for three days.

Body weight 15 to 20 kg: 200 mg once daily for 3 days; body weight 26 to 35 kg: 300 mg daily for 3 days.

Uncomplicated genital chlamydia infection and non-gonococcal infection: 500 mg once daily for 7 days.

Contraindications Hepatic impairment (Appendix 7a); hypersensitivity to erythromycin.

Precautions Pregnancy (Appendix 7c) and lactation (Appendix 7b); renal impairment, prolongation of QT interval (ventricular tachycardia reported); interactions (Appendix 6c, 6d); exacerbation of symptoms of myasthenia gravis; impaired hepatic function.

Adverse Effects Fewer gastrointestinal effects as compared to erythromycin, 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; flatulence, somnolence, angioedema; eczema, pharyngitis; arthalgia, conjunctivitis.

Storage Store protected from moisture.

Benzathine Benzyl Penicillin*

Indications *Mild to moderate infections of upper respiratory tract due to susceptible streptococci, Syphilis, prophylaxis of rheumatic fever.*

Availability **INJECTABLE SUSPENSION**- 1200,000 units/2 ml.

Dose **Streptococcal URTI:** 1.2 million unit (>27 kg) single dose (deep IM inj) after sensitivity test (AST); 0.6 million unit (<27 kg) single dose (deep IM inj) AST.

Secondary prophylaxis of Rheumatic fever: 1.2 million unit (> 27 kg) single dose (deep IM inj) after sensitivity test (AST) every 21 days; 0.6 million unit (<27 kg) single dose (deep IM inj) AST every 15 days.

Syphilis: Primary, secondary, or early latent: Single dose of 2.4 million Unit IM; Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary: 2.4 million Unit IM weekly for 3 weeks.

Contraindications Hypersensitivity, neurosyphilis.

Precautions Hypersensitivity to cephalosporins or/ and penicillins, elderly, infants, asthma, kidney disease, lactation (Appendix 7b); interactions (Appendix 6c).

Adverse effects Hypersensitivity reactions such as exfoliative dermatitis, pain at injection site, thrombophlebitis of injected vein, diarrhoea, nausea, joint pain, angioedema, serum sickness like reactions; haemolytic anaemia, interstitial nephritis.

Benzyl Penicillin

Pregnancy Category-B

Schedule H

Indications *Mild to moderate infections of upper respiratory tract due to susceptible streptococci, syphilis, prophylaxis of rheumatic fever.*

Availability **INJECTABLE SUSPENSION-** 6, 12, 24 Lac units; **INJECTABLE SUSPENSION-** 1200,000 units/2 ml.

Dose **Streptococcal URTI:** 1.2 million unit (>27 kg) single dose (deep IM inj) after sensitivity test (AST); 0.6 million unit (<27 kg) single dose (deep IM inj) AST.

Secondary prophylaxis of Rheumatic fever: 1.2 million unit (>27 kg) single dose (deep IM inj) after sensitivity test (AST) every 21 days;
0.6 million unit (<27 kg) single dose (deep IM inj) AST every 15 days.

Syphilis: Primary, secondary, or early latent: Single dose of 2.4 million Unit IM; Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary: 2.4 million Unit IM weekly for 3 weeks.

Contraindications Hypersensitivity, neurosyphilis.

Precautions Hypersensitivity to cephalosporins or/ and penicillins, elderly, infants, asthma, renal impairment (Appendix 7d), lactation (Appendix 7b); pregnancy (Appendix 7c).

Adverse Effects Hypersensitivity reactions such as exfoliative dermatitis, pain at injection site; thrombophlebitis of injected vein, diarrhoea, nausea, joint pain, angioedema, serum sickness like reactions, haemolytic anaemia, interstitial nephritis.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Cefazolin

Pregnancy Category-B

Schedule H

Indications *Respiratory tract infection; urinary tract infection; skin and soft tissue infection; biliary tract infection; bone and joint infection; endocarditis; septicaemia; preoperative prophylaxis.*

Availability **INJECTION** 125, 250, 500 mg and 1g/vial.

Dose ***Intramuscular and intravenous injection***

Adult- 1 to 4g daily in 2 to 3 divided doses.

Child- 50 to 100 mg/kg body weight every 6 h.

Contraindications Hypersensitivity and cephalosporin; colitis; lactation; pregnancy (Appendix 7c).

Precautions Renal function impairment (Appendix 7d); over growth of non-susceptible organism; interactions (Appendix 6c).

Adverse Effects Eosinophilia; diarrhoea; fever; convulsions; neutropenia, anaphylaxis, phlebitis, oral candidiasis, leucopenia; transient rise in SGOT and SGPT and alkaline phosphatase.

Storage Store protected from light and moisture at a temperature not exceeding 30°C. The constituted solution should be stored protected from light and used within 24 hours when stored at a temperature not exceeding 30°C or within 4 days when stored between 2 to 8°C.

Cefixime*

Pregnancy Category-B

Schedule H

Indications *Otitis media, respiratory tract infections, uncomplicated UTIs, effective against infections caused by Enterobacteriaceae, H. influenza species.*

Availability **TABLETS** 50, 100, 200 and 400 mg; **CAPSULES** 100 and 200 mg; **SYRUP/SUSPENSION** 50 mg/5 ml, 100 mg/5 ml.

Dose **Adult-** 200-400 mg/day as a single dose or in two divided doses.

Child- (more than 6 months) 8 mg/kg/day as a single dose or two divided doses.

Uncomplicated gonorrhea: Adult- 400 mg as a single dose.

Contraindications Hypersensitivity to cephalosporins.

Precautions History of allergy to penicillins, renal failure (Appendix 7d) or patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD), gastrointestinal disease, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).

Adverse Effects Diarrhoea, pseudomembranous colitis, loose or frequent stools, abdominal pain, nausea, dyspepsia; hypersensitivity reactions.

Storage Store protected from light and moisture at a temperature not exceeding 30°C.

Cefoperazone

Pregnancy Category-B

Schedule H

Indications *Urinary, biliary, respiratory, skin soft tissue infections, meningitis, septicemias, Pseudomonas, Salmonella typhi, B. fragilis infections.*

Availability **INJECTIONS** 0.25, 1.0, 2.0 g/vial.

Dose 25-100 mg/kg/day in 2-3 divided doses.

Contraindications Hypersensitivity, interactions (Appendix 6a).

Adverse Effects Anaphylaxis, fever, skin rashes; nephritis; granulocytopenia, and hemolytic anaemia, hypoprothrombinaemia and bleeding disorders.

Cefotaxime*

Pregnancy Category-B

Schedule H

Indications *Infections due to sensitive Gram positive and Gram negative bacteria such as bacteraemia, cellulites, intra-abdominal infections, gonorrhoea, bone or joint infections, skin and skin structure infections, urinary tract infections, septicaemias, surgical prophylaxis, endometritis, life threatening resistant/hospital acquired infections, infections in immuno-compromised patients, Haemophilus epiglottitis and meningitis.*

Availability **INJECTION** 125, 250, 500 mg, and 1g/vial.

Dose **Susceptible infections:** 1–2g by i.v or i.m injection, 8 – 12 hourly. Max.-12 g/day.

Child- 50-100 mg/kg/day.

Surgical prophylaxis: 1g by i.v or i.m injection, 30-90 minutes before procedure.

Gonorrhoea: 0.5–1g by i.m injection, as a single dose.

Septicaemia, meningitis:
Adult- 2g i.v, 6-8 hourly for 14-28 days.

Neonates- 50 mg/kg daily in 2–4 divided doses may be increased to 150–200 mg/kg daily in severe infections.

Child- 100–150 mg/kg daily in 2–4 divided doses increased up to 200 mg/kg daily in very severe infections.

Contraindications Renal disease (Appendix 7d); hypersensitivity to cephalosporins.

Precautions Impaired kidney or liver disease, colitis; history of penicillin allergy; pregnancy (Appendix 7c), lactation; diabetes.

Adverse effects Local inflammation or pain at injection site; thrombocytopenia, eosinophilia, leukopenia; pseudomembranous colitis, moniliasis, diarrhoea, candidiasis, decreased urination; seizures, headache, nausea and vomiting; jaundice; Steven's Johnson syndrome.

Storage Store protected from light at a temperature not exceeding 30°C.

Ceftazidime*

Pregnancy Category-B

Schedule H

Indications

Infections due to sensitive bacteria, especially those due to Pseudomonas spp. and including those resistant to aminoglycosides.

Availability

INJECTION 250, 500 mg, 1g and 2g vial.

Dose

Deep intramuscular and intravenous injection and infusion

Adult- 1g every 8 h or 2g every 12 h.
Severe infections: 2g every 12 h or 3g every 12 h (1g single dose by intravenous route).
Immunocompromised or meningitis patients: 150 mg/kg body weight daily in 3 divided doses (max 6g daily) given by i.v route only.

Elderly- Usual max dose of 3g daily.

Child- Up to 2 months; 25 to 60g/kg body weight in two divided doses. Over 2 months: 30 to 100 mg/kg body weight in 2 to 3 divided doses.

Contraindications

Cephalosporin hypersensitivity; porphyria.

Precautions

Penicillin sensitivity; renal impairment; lactation (Appendix 7b); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; interactions (Appendix 6b, 6c); pregnancy (Appendix 7c); fall in prothrombin activity, colitis.

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, confusion, hypertonia and dizziness; phlebitis, angioedema, myoclonia, candidiasis, transient elevation of blood urea and serum creatinine.

Storage

Store in sterile containers sealed so as to exclude micro-organisms protected from moisture at a temperature not exceeding 30°C.

Ceftriaxone*

Pregnancy Category-B

Schedule H

Indications

Serious infections due to sensitive bacteria, including septicaemia, pneumonia and meningitis; surgical prophylaxis; prophylaxis of meningococcal meningitis; gonorrhea; bone and joint infection.

Availability

INJECTION 125, 250, 500 mg, 1g and 2g vial.

Dose

Intramuscular and intravenous injection or infusion

Adult- Urinary tract infection, pneumonia, pelvic inflammatory disease, prophylaxis of surgical infections and meningitis: 4g initially once daily for 10 days or up to 72 h after fever disappears.

Typhoid: 4g daily for two days followed by 2g daily for next two days. 1 to 2g daily is used for any other type of condition.

Child- Meningitis: 75 to 100 mg/kg body weight for 7 to 9 days.

Typhoid: 5 mg/kg body weight for 7 days. 50 to 75 mg/kg body weight is used in case of any other condition (max 2g/day).

Contraindications

Cephalosporin hypersensitivity; porphyria; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding.

Precautions

Penicillin sensitivity; severe renal impairment; hepatic impairment if accompanied by renal impairment (Appendix 7a); 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; lactation (but appropriate to use, see Appendix 7b); pregnancy (Appendix 7c); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; interactions (Appendix 6b, 6c); phrophylactic indication, patients with impaired vit K synthesis, monitoring of prothrombin time is recommended.

Adverse Effects

Diarrhoea, nausea and vomiting, abdominal discomfort, headache; antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis and cholestatic jaundice; elevation of SGOT and SGPT; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, confusion, hypertonia and dizziness; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated, or those who are immobilized) or in gall bladder-consider discontinuation if symptomatic; rarely, prolongation of prothrombin time, pancreatitis; local reaction, hypersensitivity.

Storage

Store protected from light at a temperature not exceeding 30°C.

Cephalexin*

Pregnancy Category-B

Schedule H

Indications

Respiratory tract infections; otitis media; skin and skin structure infections; genitourinary tract infection; bone infection.

Availability

CAPSULES/TABLETS 125, 250 and 500 mg; 125 mg Kid tablets; 250 mg **DT**; **DRY SYRUP** 125 and 250 mg/5 ml.

Dose

To be given preferably on empty stomach.

Adult- 250 mg every 6 h or 500 mg every 8 to 12 h, increased to 1 to 1.5g every 6 to 8 h for severe infections.

Prophylaxis of severe urinary tract infection: 125 mg at night.

Child- 25 mg/kg body weight daily in divided doses doubled for severe infections (max. 100 mg/kg body weight daily); Under 1year: 125 mg every 12 h; 1 to 5 years: 125 mg every 8 h; 5 to 12 years: 250 mg every 8 h.

Contraindications

Cephalosporin hypersensitivity.

Precautions

Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, renal impairment; lactation; false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; poor nutritional state; pregnancy (Appendix 7c).

Adverse Effects

Diarrhoea and rarely, antibiotic-associated colitis (more likely with higher doses), nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions with rashes, fever and arthralgia and anaphylaxis; Stevens-Johnson syndrome, toxic epidermal necrolysis reported; disturbances in liver enzymes, transient hepatitis and cholestatic jaundice; other side-effects reported include eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia and dizziness; dyspnoea, colitis, increased blood urea, creatinine, alkaline phosphatase, bilirubin, LDH.

Storage

Store protected from light and moisture at a temperature not exceeding 30°C.

Chloramphenicol* (Refer Page No. 551)

Pregnancy Category-C

Schedule H

Indications

Severe life-threatening infections, particularly those caused by Haemophilus influenzae and typhoid fever; cerebral abscess; mastoiditis; relapsing fever; gangrene; granuloma inguinale; listeriosis; severe melioidosis; plague; psittacosis; tularaemia; Whipple's disease; septicaemia; empirical treatment of meningitis; ocular infection.

Availability

CAPSULES 250 and 500 mg; **SYRUP** 125 mg/5 ml; **INJECTION** 250 and 500 mg/vial.

Dose

Oral, intramuscular or intravenous injection or infusion

Adult- 50 mg/kg body weight in four divided doses (can be doubled in very severe infections, septicaemia, meningitis, reduce as soon as clinically indicated).

Child- Haemophilus epiglotitis and pyrogenic meningitis: 50 to 100 mg/kg body weight daily in divided doses (can be doubled in severe infections, reduce as soon as clinically indicated).

Contraindications Pregnancy (Appendix 7c); porphyria; blood dyscrasias, preexisting bone marrow depression; hypersensitivity; patients receiving radiation therapy.

Precautions Avoid repeated courses and prolonged use; reduce dose in hepatic impairment (Appendix 7a) and severe renal impairment; blood counts required before and during treatment; monitor plasma concentrations in neonates (see below); lactation (Appendix 7b); interactions (Appendix 6c); regular blood count; over growth of non-susceptible organism may occur; seizure disorders.

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 baby syndrome (vomiting, greenish diarrhoea, abdominal distension, hypothermia, pallid cyanosis, irregular respiration, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism; also reported in infants born to mothers treated in late pregnancy; ocular irritation, angioneuretic edema.

Storage **Capsule:** Store protected from moisture. **Syrup and Injection:** Store protected from light and moisture.

Ciprofloxacin* (Refer Page No. 552)

Pregnancy Category-C

Schedule H

Indications *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.*

Availability **TABLETS** 100, 250, 500 and 750 mg; **INFUSION** 50, 100 and 200 ml (2 mg/ml).

Dose ***Oral***

Adult- Urinary tract infection, respiratory tract infection: 250 to 500 mg, twice daily. Severe respiratory tract infections: up to 750 mg twice daily (however in acute uncomplicated cystitis in women 100 mg twice daily for three days).

Chronic prostatitis: 500 mg twice daily for 28 days.
Gonorrhoea: 500 mg as a single dose.

Child- Not recommended.

Intravenous infusion (30 to 60 min)

Adult- Urinary tract infection, ENT infection, skin, soft tissue and bone infection, joint infection, gastrointestinal tract infection, severe systemic infection, gonorrhea, surgical prophylaxis and septicaemia; 100 to 200 mg twice daily by slow intravenous injection or infusion.

Contraindications

History of tendon disorders related to quinolone use; exposure to strong sunlight, hypersensitivity to quinolones derivatives; tizanidine therapy.

Precautions

History of epilepsy or conditions that predispose to seizures, G-6-PD deficiency, myasthenia gravis (risk of exacerbation), pregnancy (Appendix 7c), lactation (Appendix 7b), 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; renal failure (Appendix 7d); avoid excessive alkalinity of urine and ensure adequate fluid intake as there is risk of crystalluria; interactions (Appendix 6c); cerebral arteriosclerosis, anxiety, paranoia, erythema, blistering.

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.

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

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; if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur discontinue; arthralgia.

Storage

Eye drops and Tablet: Store protected from light. **Injection:** Store protected from light at a temperature not exceeding 30°C. The container should not be allowed to freeze.

Clarithromycin

Pregnancy Category-C

Schedule H

Indications

For the treatment of bacterial infections (pharyngitis/tonsillitis, sinusitis, bronchitis, pneumonia, uncomplicated skin and skin structure infections) caused by H. influenzae, M. catarrhalis, M. pneumoniae, S. pneumoniae, C. pneumoniae, S. aureus, S. pyogenes, Mycobacterium avium and Mycobacterium intracellulare.

Availability

TABLETS 250 and 500 mg ; 125 mg DT.

SUSPENSION 125 mg/5 ml

Dose

Oral

Adult- 250 mg to 500 mg twice a day for 7 to 14 days increase in severe infections to 500 mg every 12 h up to 14 days.

Child- Body weight under 8 kg: 7.5 mg/kg body weight twice daily; 8 to 11 kg: 62.5 mg twice daily; 30 to 40 kg: 250 mg twice daily.

Contraindications

Hypersensitivity to clarithromycin; cephalosporin.

Precautions Neonate under 2 weeks (risk of hypertrophic pyloric stenosis); predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); avoid in porphyria; hepatic impairment; renal impairment; pregnancy (not known to be harmful) (Appendix 7c); lactation (only small amounts in milk); interactions (Appendix 6c); myasthenia gravis.

Adverse Effects Nausea, vomiting, abdominal discomfort, diarrhoea (antibiotic-associated colitis reported); less frequently urticaria, rashes and other allergic reactions; reversible hearing loss reported after large doses; cholestatic jaundice, pancreatitis, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis also reported, dyspepsia, tooth and tongue discolouration, smell and taste disturbances, stomatitis, glossitis and headache; less commonly hepatitis, arthralgia and myalgia; rarely, tinnitus; very rarely, pancreatitis, dizziness, insomnia, nightmares, anxiety, confusion, psychosis, paraesthesia, convulsions, hypoglycaemia, renal failure, leucopenia and thrombocytopenia; on intravenous infusion, local tenderness, phlebitis.

Storage Store protected from moisture.

Clindamycin*

Pregnancy Category-B

Schedule H

Indications *Respiratory tract infections, penicillin resistant staphylococcal infections and many anaerobes such as bacteroides, skin, soft tissue and dental infections.*

Availability **TABLETS/CAPSULES** 150 & 300 mg; **SYRUP** 4 ml (150 mg/ml); **INJECTION** 2 ml (150 mg/ml); **CREAM/GEL/OINTMENT** 10g (1%w/w); **LOTION** 25 ml (1%w/v).

Dose ***Oral***

Serious anaerobic infections
Adult: 150-300 mg 6 every hr; for more severe infection: 300 to 450 mg every 6 hr.
Child: 2-4 mg/kg every 6 hr; for more severe infection: 3-6 mg/kg every 6 hr; 10 kg: 37.5 mg every 8hr.
Prophylaxis of endocarditis 600 mg 1 hr before dental procedure.

Intravenous/Intramuscular
Serious anaerobic infections
Adult: 0.6-2.7 g/day in 3-4 divided doses, up to 4.8 g/day for severe infections.
Child: 20-40 mg/kg daily in 3-4 divided dose.
Neonate: 15-20 mg/kg daily in 3-4 divided dose
Toxic shock syndrome
Adult: 900 mg every 8 hr along with penicillin G or ceftriaxone.
Pelvic inflammatory disease
Adult: 900 mg every 8 hr along with gentamicin.
Vaginal
Bacterial vaginosis
As pessary or 2% cream: 100 mg once nightly for 3-7 days.
Topical
Acne
As 1% preparation: Apply twice daily.

Contraindications Hypersensitivity, meningitis as it has less penetration into CNS, pseudomembranous colitis.

Precautions Hepatic and renal impairment, pregnancy and lactation, GI disease, elderly, atopic patients, regular monitoring of blood counts, in conjuction with antibiotic therapy, pregnancy (Appendix 7c), interactions (Appendix 6c).

Adverse Effects Urticaria, rashes, contact dermatitis, exfoliative and vesiculous dermatitis, local irritation abdominal pain, oesophagitis, nausea, vomiting, diarrhoea, jaundice and liver abnormalities, eosinophilia, erythema multiforme, thrombophloebitis, gasping syndrome (premature infants and neonates) due to preservative benzoyl alcohol in parenteral formulation, pseudomembranous colitis, azotemia, oliguria, proteinuria.

Storage Store protected from moisture

Cloxacillin

Pregnancy Category-B

Schedule H

Indications *Multibacillary (MB) leprosy; type 2 lepra reactions; gram positive infection including resistant staphylococci.*

Availability **CAPSULES** 250 and 500 mg; **INJECTION** 250 and 500 mg/vial; **DRY SYRUP** 125 mg/5 ml.

Dose ***Oral***

Adult- 250-500 mg every 6 h at least 30 min. before food. Osteomyelitis; upto 8g daily in 2 to 3 divided doses. Surgical prophylaxis; 1 to 2g at induction thereafter up to 4 further doses each of 500 mg may be given every 6 h.

Slow intravenous injection or infusion

Adult- Surgical prophylaxis; 1 to 2g at induction thereafter up to 4 further doses each of 500 mg may be given every 6 h.

Child- High risk procedures; Under 2 years; quarter adult dose. 2 to 10 years; half adult dose.

Contraindications Hypersensitivity to penicillins (see notes above).

Precautions History of allergy (see notes above); renal and hepatic impairment (Appendix 7a); heart failure; lactation (Appendix 7b); pregnancy (Appendix 7c).

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.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Cotrimoxazole*
(Trimethoprim + Sulphamethoxazole)

Pregnancy Category-C

Schedule H

Indications *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.*

Availability **TABLETS** (TMP + SMZ) 80 mg + 400 mg and 160 mg + 800 mg; **SUSPENSION** 40 mg TMP + 200 mg SMZ/5 ml.

Dose **Adult-** 1 to 2 tablets twice daily for 7-14 days (160 + 800 mg).

Child- Suspension 5 ml twice daily (40 + 200 mg). infant 2.5 ml.

Contraindications Hypersensitivity to sulfonamides or trimethoprim; porphyria; marked liver parenchymal damage, blood dyscrasias, severe renal insufficiency.

Precautions Renal impairment; hepatic impairment (avoid if severe; Appendix 7a); 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; G-6-PD deficiency; lactation (Appendix 7b); avoid in infants under 6 weeks; elderly.; pregnancy (Appendix 7c); interactions (Appendix 6c).

Adverse Effects Nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, pruritus, photosensitivity reactions, exfoliativedermatitisanderythemanodosum; 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; elevation of transaminase and bilirubin; skin rashes.

Storage Store protected from light and moisture. Suspension should not be allowed to freeze.

Doxycycline* (Refer Page No. 178)

Pregnancy Category-D

Schedule H

Indications *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; 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.*

Availability **TABLETS/CAPSULES** 100 and 200 mg; **SYRUP** 25 mg/5 ml.

Dose ***Oral***

Severe infections including refractory urinary tract infection: 200 mg daily.
Early syphilis: 100 mg twice daily for 14 days. Latent syphilis: 200 mg twce daily for 28 days.
Uncomplicated genital Chlamydia, non-gonococcal urethritis: 100 mg twice daily for 7 days.

Child- Only if alternate antibacterial cannot be given 5 mg/kg body weight in two divided doses.

Contraindications Pregnancy (Appendix 7c); children (see notes above); porphyria; systemic lupus erythematosus; hypersensitivity to tetracycline.

Precautions Avoid exposure to sunlight or sunlamps-photosensitivity reported; renal impairment; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6c 6d); predisposition to candidiasis.

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; erythematous rashes, nasophryngitis, sinusitis, increased blood glucose levels, haemolytic anaemia, neutropenia.

Storage Store protected from light and moisture at a temperature not exceeding 30°C.

Erythromycin*

Pregnancy Category-B

Schedule H

Indications *Alternative to penicillin in hypersensitive patients; pneumonia; legionnaires' disease; syphilis; chancroid; chlamydia; non-gonococcal urethritis; prostatitis; lymphogranuloma venereum; campylobacter enteritis; relapsing fever; diphtheria and whooping cough prophylaxis upper respiratory tract infection, acne vulgaris, sycosis, vulgaris.*

Availability — **TABLETS** 125, 250 and 500 mg plain; 125 DT; **SYRUP** 125 mg/5 ml; **OINTMENT** 2 and 3% w/w; **CREAM** 3% w/w.

Dose — ***Oral***

Adult and child over 8 years- 250 to 500 mg every 6 h or 0.5 to 1g every 12 h upto 4g daily in severe infections.

Child- 1 month to 2 years; 12.5 mg/kg body weight every 6 h; 2 to 8 years 250 mg every 6 h (doses doubled for severe infections).

Early syphilis: 500 mg three times daily for 14 days.

Contraindications — Hypersensitivity to erythromycin or other macrolides; porphyria; myasthenia gravis.

Precautions — Hepatic impairment (Appendix 7a) and renal impairment (Appendix 7d); prolongation of the QT interval (ventricular tachycardia reported); pregnancy (Appendix 7c); (not known to be harmful); lactation (Appendix 7b); interactions (Appendix 6c).

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; burning sensation, itching, anorexia.

Storage — Store protected from light at a temperature not exceeding 30°C.

Framycetin*

Schedule H

Indications — *Bacterial skin infections, burns, ENT infections, surgical infections, traumatic injury, conjunctivitis, blepharitis.*

Availability — **CREAM** 1% - 5, 15 and 40g; **DROPS** 5 ml (0.5%); **DRESSING** 1%; **POWDER** 15g.

Dose — **Topical**

Skin infections: **Adult-** as 1% dressing.

Ophthalmic

Blepharitis along with conjunctivitis:
Adult- as 0.5 % ointment, apply 2-3 times daily.

Otitis externa

Adult- 0.5% drops.

Contraindications Tuberculosis, glaucoma, perforated tympanic membrane, fungal, viral or resistant bacterial infections of eye, hypersensitivity.

Precautions Pregnancy, ototoxicity due to systemic absorption may occur if applied on large areas in children, elderly and patients with renal failure, avoid prolonged use, interactions (Appendix 6c).

Adverse effects Ototoxicity, gastrointestinal symptoms, inflammation, transient irritation, contact dermatitis, burning sensation, pruritus.

Storage Store protected from light and moisture at a temperature not exceeding 30°C. If the material is sterile, the container should be tamper-evident and sealed so as to exclude micro-organisms.

Gentamicin* (Refer Page No. 553)

Pregnancy Category-C

Schedule H

Indications *Pneumonia; cholecystitis; peritonitis; septicaemia; acute pyelonephritis; prostatitis; skin infections; pelvic inflammatory disease; endocarditis; meningitis; listeriosis; tularaemia; brucellosis; plague; surgical prophylaxis; ocular bacterial infection.*

Availability **EYE DROPS** 0.3% w/v, **CREAM** 15g (0.1% w/w); **INJECTION** 2 ml ampoule (40 mg/ml), 2 and 10 ml vials (40 mg/ml).

Dose ***Intravenous infusion***

Once daily dose regime; 5 to 7 mg/kg body weight, then adjust as per serum gentamicin concentration.

Intramuscular or slow intravenous injection over at least 3 min.

Multiple daily dose regimen: 3 mg/kg body weight divided into 8 hly doses.

Child- 2 weeks to 12 years; 2 mg/kg body weight 8 hly.

Contraindications Myasthenia gravis.

Precautions Renal impairment (Appendix 7d), 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; interactions (Appendix 6c); purulent discharge, discontinue if pain/inflammation becomes aggravated; pregnancy (Appendix 7c).

Adverse Effects Vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy; antibiotic-associated colitis, also nausea, vomiting, rash; bacterial/fungal corneal ulcers, ocular burning or irritation, thrombocytopenia, joint pain.

Storage Store protected from moisture if it is intended for use in the manufacture of parenteral preparations.

Imipenem + Cilastatin

Pregnancy Category-C

Schedule H

Indications *Severe aerobic and anaerobic Gram-positive and Gram-negative infections in hospital -acquired infections (not indicated for CNS infections), including infections caused by resistant Pseudomonas and Acinetobacter species.*

Availability

INJECTION Imipenem	+	Cilastatin
125 mg	+	125 mg vial
250 mg	+	250 mg vial
500 mg	+	500 mg vial
1g	+	1g vial
2g	+	2g vial

Dose ***Intravenous infusion in terms of imipenem***

Adult- 2g daily in 2 to 3 divided doses. Less susceptible organism may be given up to 3 to 4 divided doses (max 4g daily).

Surgical prophylaxis: 1g for induction, repeated every three h, supplemented in high risk surgery by doses of 500 mg for 8 to 16 h.

Child- 3 months and older: 60 mg/kg body weight in four divided doses. Over 40 kg: adult dose.

Contraindications Hypersensitivity to beta-lactam antibiotics; local anaesthetics of the amide type and in patients with severe shock or heart block.

Precautions Renal impairment; CNS disorders, such as epilepsy; lactation (Appendix 7b); interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting, diarrhoea; antibiotic-associated colitis; taste disturbances; tooth or tongue discolouration, hearing loss; blood disorders, (decreased haematocrit, increased prothrombin time) positive Coombs' test; allergic reactions including rash, pruritus, urticaria, erythema multiforme (Steven's-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; increase in serum creatinine and blood urea; red coloration of urine in children; erythema, pain and induration and thrombophlebitis at injection sites; bone marrow depression.

Storage Store protected from moisture in a single dose or multi dose container.

Meropenem

Pregnancy Category-B

Schedule H

Indications *Nosocomial infection like septicemia, febrile neutropenia, intraabdominal and pelvic infection etc caused by cephalosporins resistant bacteria, meningitis, cystic fibrosis.*

Availability **INJECTIONS** 0.125, 0.250, 0.5, 1 g/vial.

Dose **Adult-** 0.5-2 g or 10-40 mg/kg by slow i.v injection 8 hourly.

Neonate (less than 7 days)- 20 mg/kg 12 hourly.

7-28 days- 20 mg/kg 8 hourly.

1-3 months- 10 mg/kg 8 hourly.

> 3 months- 10- 20 mg/kg 8 hourly.

Meningitis: Adult- 2g 8 hourly.

Child- (> 3 months)- 40 mg/kg 8 hourly.

Contraindications Hypersensitivity.

Precautions Renal insufficiency, neurological disorders, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms, pregnancy (Appendix 7c), lactation, history of hypersensitivity to other β-lactam antibiotics; interactions (Appendix 6c).

Adverse Effects Inflammation at the injection site; nausea, vomiting, headache, rash; diarrhoea, thrombophlebitis, anaphylaxis, pseudomembranous colitis, disturbances in LFTs.

Metronidazole* (Refer Page No. 106)

Pregnancy Category-B

Schedule H

Indications *Anaerobic bacterial infections including gingivitis, pelvic inflammatory disease, tetanus, peritonitis, brain abscess, necrotizing pneumonia, antibiotic-associated colitis, leg ulcers and pressure sores and surgical prophylaxis; bacterial vaginosis; tissue nematode infections; trichomonal vaginitis, amoebiasis and giardiasis; Helicobacter pylori eradication.*

Availability **TABLETS** 200 and 400 mg; **SUSPENSION** 200 mg/5 ml; **INJECTION** 100 ml infusion (5 mg/ml).

Dose ***Oral***

Adult- Amoebiasis: 400 to 800 mg every 8 h for 5 to 7 days. **Giardiasis**L: 200 mg three times a day for 7 to 10 days or **intravenous injection** 500 mg 8 hly for 7 days.

Child- Amoebiasis: Below 12 years; 7.5 mg/kg body weight. 12 years and above; 35 to 50 mg/kg body weight daily in three divided doses.

Contraindications Chronic alcohol dependence; first trimester of pregnancy.

Precautions Disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 7a); lactation (Appendix 7b); clinical and laboratory monitoring in courses lasting longer than 10 days; interactions (Appendix 6a, 6c, 6d); pregnancy (Appendix 7c); phenobarbitone, history of blood dyscrasias.

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; paresthesia.

Storage Store protected from light and moisture. Store injection in a single dose container.

Nalidixic Acid

Pregnancy Category-C

Schedule H

Indications *Urinary-tract infections; shigellosis.*

Availability **TABLETS** 250, 500 mg and 1g; **SUSPENSION** 300 mg/5 ml.

Dose ***Oral***

Adult- 1g every 6 h for 7 days. Reduced in chronic infection to 600 mg every 6 h.

Child- Over 3 months: max 50 mg/kg body weight in divided doses, in prolonged therapy, reduced to 30 mg/kg body weight daily.

Contraindications Hypersensitivity; children <3 years age, porphyria; convulsive disorder.

Precautions History of epilepsy or conditions that predispose to seizures; G-6-PD deficiency; myasthenia gravis (risk of exacerbation); pregnancy (Appendix 7c); lactation (Appendix 7b); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely, tendon damage-discontinue at first sign of pain or inflammation and rest affected limb; porphyria; hepatic impairment; renal impairment; false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks; interactions (Appendix 6c); cerebro-arterial sclerosis.

Adverse Effects Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely, antibiotic-associated colitis), headache, dizziness, weakness, sleep disorders; rash (rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis) and pruritus; less frequently anorexia, increase in blood urea and creatinine; metabolic acidosis; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia, raised intracranial pressure, cranial nerve palsy; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia and anaphylaxis; blood disorders (including eosinophilia, leukopenia, thrombocytopenia); disturbances in vision, taste, hearing and smell; 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.

Storage Store protected from light and moisture.

Nitrofurantoin*

Pregnancy Category-B

Schedule H

Indications *Urinary-tract infections; cystitis.*

Availability **TABLETS** 50, 100 and 200 mg.

Dose **Adult-** 50 mg every 6 h with food for 3-7 days.

Child- Over 3 months: 3 mg/kg body weight daily in four divided doses. Severe chronic recurrent infections: 100 mg every 6 h with food for 7 days, discontinue or reduce dosage in case of nausea.

Contraindications Impaired renal function; infants less than 3 months; G-6-PD-deficiency including lactation of affected infants (Appendix 7b); pregnancy, at term (Appendix 7c); porphyria; anuria, oliguria, labour and delivery, neonates; interactions (Appendix 6a, 6d).

Precautions Pulmonary disorders or hepatic impairment (Appendix 7a); 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.

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; dyspepsia, dizziness, nystagmus.

Storage Store protected from light and moisture.

Norfloxacin

Pregnancy Category-C

Schedule H

Indications *Uncomplicated gonorrhea; chronic bacterial prostatitis; complicated UTI; gastroenteritis; conjunctivitis.*

Availability **TABLETS** 200, 400, 800 mg; 100 mg DT; **SUSPENSION** 100 mg/5 ml.

Dose ***Oral***

Urinary tract infection and upper respiratory tract infections: 200 to 400 mg daily preferably in the morning. Increase if necessary in upper urinary tract infection to 400 mg twice daily. Uncomplicated gonorrhea: 400 mg as a single dose.

Uncomplicated genital chlamydia infections, non-gonococcal urethritis: 400 mg daily in single dose for 7 days or divided doses for 7 days.

Contraindications History of hypersensitivity, tendinitis.

Precautions Should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G-6-PD deficiency, myasthenia gravis (risk of exacerbation), in renal impairment; during lactation. Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). Quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time, organ system assessment, haemolytic reaction, pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely, antibiotic-associated colitis), headache, dizziness, sleep disorders; rash (rarely, Stevens-Johnson syndrome and toxic epidermal necrolysis) and pruritus. Less frequent side-effects include anorexia, increase in blood urea and creatinine; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, tremor, paraesthesia, hypoaesthesia; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia and anaphylaxis; blood disorders (including eosinophilia, leucopenia, thrombocytopenia); disturbances in vision, taste, hearing and smell. The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur; rash, heart burn, abdominal cramps, irritability.

Storage Store protected from light and moisture.

Ofloxacin*

Pregnancy Category-C

Schedule H

Indications *Acute uncomplicated cystitis, community acquired pneumonia, acute exacerbation of chronic bronchitis.*

Availability **TABLETS** 100, 200 and 400 mg; **SYRUP** 30 ml (50 mg/5 ml, 100 mg/5 ml); **INJECTION** 100 ml (2 mg/ml);
EYE DROPS 0.3% w/v.

Dose ***Oral***

Community acquired pneumonia:
Adult- 400 mg twice daily for 10 days.

Pelvic inflammatory disease:
Adult- 400 mg twice daily for 14 days.

Complicated UTI:
Adult- 200 mg twice daily for 10 days.

Parenteral

Complicated UTI:
Adult- 200 mg daily by i.v infusion over atleast 30 minutes, max. 400 mg twice infused over at least 1 h.

Septicaemia, lower respiratory tract infection:
Adult- 200 mg twice daily by i.v infusion over at least 30 minutes, max. 400 mg twice daily infused over at least 1 h.

Bacterial corneal ulcer:
Adult- 0.3%, 1-2 drops every 30 minutes.

Ophthalmic

Bacterial conjunctivitis:
Adult- 0.3%, 1-2 drops every 2-4 h.

Child- >1year, 1-2drops every 2-4 h.

Contraindications Hypersensitivity.

Precautions Patients with epilepsy, kidney disease, tendon problem, nervous system problem, liver disease (Appendix 7a), limit alcohol intake, pregnancy (Appendix 7c); lactation (Appendix 7b).

Adverse effects Sinus tachycardia, hallucination, Steven's Johnson syndrome, seizure; dizziness, headache, nausea, vomiting, diarrhoea; insomnia, pruritus, photosensitivity.

Storage **Tablets:** Store protected from light and moisture. **Eye Drops:** Store protected from light.

Phenoxymethyl Penicillin (Penicillin V)

Pregnancy Category-B

Schedule H

Indications *Streptococcal pharyngitis; otitis media; erysipelas; mouth infections; secondary prophylaxis of rheumatic fever; post-splenectomy prophylaxis.*

Availability **TABLETS** 125 and 250 mg.

Dose **Adult-** 500 mg every 6 hour increased to 750 mg every 6 h in severe cases.

Child- up to 1 year: 62.5 mg every 6 h.
1 to 5 years: 125 mg every 6 h.
6 to 12 years: 250 mg every 6 h.

Contraindications Hypersensitivity to penicillins (see notes above); serious infections (see notes above).

Precautions History of allergy (see notes above); lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6c); cross sensitivity with cephalosporins may occur.

Adverse Effects Hypersensitivity reactions including urticaria, serum sickness reaction; joint pain, rash, angioedema, anaphylaxis (see notes above); nausea and diarrhoea; epigastric distress, skin eruptions; haemolytic anaemia.

Storage Store protected from moisture.

Piperacillin + Tazobactam

Pregnancy Category-B

Schedule H

Indications *Nosocomial pneumonia, infections following burns, urinary tract infections.*

Availability **INJECTIONS** Piperacillin 4g +Tazobactam 0.5g Piperacillin 2g + Tazobactam 0.25g, Piperacillin 1g +Tazobactam 0.0125g.

Dose 4.5g (Piperacillin 4g + Tazobactam 0.5g) every 6 h for 7-14 days.

Contraindications Hypersensitivity to penicillins.

Precautions Pregnancy (Appendix 7c), lactation; prolonged treatment may increase super infections, interactions (Appendix 6c).

Adverse Effects Hypersensitivity reactions like rash, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis, Steven's-Johnson syndrome, and anaphylaxis.

Storage Store below 25°C.

Procaine Benzyl Penicillin (Procaine Penicillin G)

Pregnancy Category-B

Schedule H

Indications *Syphilis; anthrax; childhood pneumonia; diphtheria carrier state; cellulitis; mouth infections; bites.*

Availability **VIALS** 5 and 10 lac units.

Dose ***Intramuscular and intravenous injection or infusion***

Adult- Streptococcal infection and pyroderma: single dose 12 lac units. Syphilis: 24 lac units every week for three weeks. Rheumatic fever: 12 lac units every 3 to 4 weeks.

Contraindications Hypersensitivity to penicillins (see notes above); intravascular injection.

Precautions History of allergy (see notes above); renal failure; pregnancy (Appendix 7c).

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 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.

Storage The constituted solution should be used immidiately after preparation but in any case within the period recommended by the manufacturer.

Roxithromycin

Pregnancy Category-B

Schedule H

Indications *Susceptible infections; pneumonia, acute bronchitis, sinusitis, pharyngitis, tonsillitis, genital infection.*

Availability **TABLETS** 150 and 300 mg; **SUSPENSION** 50 mg/ml; **DROPS** 10 ml (25 mg/ml).

Dose **Adult-** 150 mg twice a day at least 15 min before meals.

Child- 5 to 8 mg/kg body weight in two divded doses for not more than 10 days.

Contraindications Concomitant use with ergot alkaloid type compounds.

Precautions Hepatic dysfunction; paediatrics (reduce dose); interactions (Appendix 6d); pregnancy (Appendix 7c).

Adverse Effects Diarrhoea; vomiting; nausea; transient rise in liver transaminase; skin rash; gastralgia.

Storage Store protected from light and moisture.

Sulphadiazine*

Pregnancy Category-C

Schedule H

Indications

Prevention of recurrences of rheumatic fever; toxoplasmosis; prophylaxis of meningococcal infections.

Availability

TABLET 500 mg.

Dose

Oral

Adult- 500 mg twice a day.

Child- Up to 8 years: 125 mg twice daily. 8 to 12 years: 250 mg twice daily.

Contraindications

Hypersensitivity to sulfonamides; porphyria; severe renal hepatic impairment, blood dyscrasias, elderly.

Precautions

Hepatic impairment (avoid if severe; Appendix 7a); renal impairment; 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; rashes-discontinue immediately; predisposition to folate deficiency; elderly; asthma; G-6-PD deficiency; lactation (Appendix 7b); avoid in infants under 6 weeks; interactions (Appendix 6d); pregnancy (Appendix 7c).

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, ataxia, tinnitus, vertigo, dizziness, hallucinations, and electrolyte disturbances; convulsions, hypoprothrombinemia, methaemoglobinemia, anorexia, pancreatitis.

Storage

Store protected from light and moisture.

Tetracycline (Refer Page No. 555)

Pregnancy Category-D

Schedule H

Indications

Rocky Mountain spotted fever; typhus; Q fever; rickettsial pox; tick fever caused by Rickettsiae; respiratory tract infections caused by Mycoplasma pneumonia; chlamydia infection; nongonococcal urethritis; chancroid; plague; tularemia; cholera; brucellosis; bartonellosis; granuloma inguinale; haemophilus and kleibsella infections; psittacosis.

Availability

CAPSULES/TABLETS 250 and 500 mg.

Dose

Adult- 250 mg every 6 h, increase to 500 mg every 6 to 8 h in severe infections.

Non-gonococcal urethritis: 500 mg every 6 h for 7 to 14 days (21 days if failure or relapse after course is seen).

To be taken with plenty of fluid while sitting or standing.

Child- 25 to 50 mg/kg body weight, daily in three divided doses. Avoid in children below 8 years.

Contraindications

Deposition of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia and they should not be given to children under 12 years, or to pregnant (Appendix 7c) or lactating women (Appendix 7b). However, doxycycline may be used in children for treatment and post-exposure prophylaxis of anthrax when an alternative antibacterial cannot be given (unlicensed indication). With the exception of doxycycline and minocycline, the tetracyclines may exacerbate renal failure and should not be given to patients with kidney disease; hypersensitivity; interactions (Appendix 6c, 6d)

Precautions

Used with caution in patients with hepatic impairment or those receiving potentially hepatotoxic drugs. Tetracyclines may increase muscle weakness in patients with myasthenia gravis and exacerbate systemic lupus erythematosus; antacids and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines; milk also reduces the absorption of tetracyclines, demeclocyclines and oxytetracycline; cerebrovascular sensitisation, maculopapular rashes, increased blood urea nitrogen, anaemia.

Adverse Effects Nausea, vomiting, diarrhoea (antibiotic-associated colitis reported occasionally), dysphagia and oesophageal irritation. Other rare side-effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity (particularly with demeclocycline) and hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis). Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment); bulging fontanelles have been reported in infants; anaemia.

Storage Store protected from light and moisture.

Trimethoprim

Pregnancy Category-C

Schedule H

Indications *Urinary-tract infections; bronchitis.*

Availability Refer cotrimoxazole above.

Dose ***Oral***

Adult- 200 mg every 12 h.

Child- 1 month to 12 years: 4 mg/kg body weight (max. 200 mg) every 12 h. 6 weeks to 6 months: 25 mg every 12 h.

Contraindications Blood disorders; porphyria; hypersensitivity.

Precautions Renal impairment; lactation (Appendix 7b); predisposition to folate deficiency; elderly; blood counts on long-term therapy (but practical value not proven); neonates (specialist supervision required); pregnancy (Appendix 7c).

Adverse Effects Rashes, pruritus; depression of haematopoiesis; gastrointestinal disturbances including nausea and vomiting; rarely, exfoliative dermatitis and toxic epidermal necrolysis, photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis; erythema, multiforme, elevation of transaminase and bilirubin.

Storage Store protected from light and moisture.

Vancomycin*

Pregnancy Category Oral Capsules- B
Parenteral Formulation- C

Schedule H

Indications — *Methicillin-resistant staphylococcal pneumonia; staphylococcal meningitis; endocarditis prophylaxis (with gentamicin).*

Availability — **TABLETS** 500 mg; **INJECTION** 250 mg, 500 mg and 1g/vial; **CAPSULE** 125 and 250 mg.

Dose — **Adult-** 1 to 1.5g every 12 h.

Elderly over 65 years; 500 mg every 12 h or 1g once daily.

Child- Over 1 month; 15 mg/kg body weight every 8 h (max. 2g daily).

Note: Oral for antibiotic associated colitis, 125 mg every 6 h for 7 to 10 days. Not very common therapy.

Contraindications — Allergy to corn/corn products, hypersensitivity.

Precautions — Avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects); rotate infusion sites; renal impairment (Appendix 7d); 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; lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6c); Pseudomembranous colitis.

Adverse Effects — Nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (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; hypotension, pruritus, haematopoitic flebitis.

Storage — Store in an air tight container protected from light.

9.3 Antifilarial Drugs

Loiasis:

Loiasis is an infection with the filarial nematode *Loa loa* and is transmitted by the biting of tabanid fly *Chrysops*. Diethylcarbamazine is effective against both adult worms and larvae; a single weekly dose is normally effective as prophylaxis. During individual treatment, particularly of persons with heavy microfilaraemia (>50 000 microfilariae/ml blood), a condition simulating meningoencephalitis occasionally occurs. This probably results from sludging of moribund microfilariae within cerebral capillaries. The frequency of meningoencephalitis associated with diethylcarbamazine therapy of loiasis is reported as 1.25%, with a mortality rate of about 50% in affected patients; treatment with diethylcarbamazine should be stopped at the first sign of cerebral involvement (and specialist advice sought). Permanent cerebral damage is common among patients who survive and this possibility should be considered when deciding on treatment. Treatment of heavily infected patients should thus begin at low dosage and corticosteroid and antihistamine cover should be provided for the first 2 to 3 days.

Lymphatic Filariasis:

Lymphatic filariasis is caused by infection with *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi* or *B. timori* (brugian filariasis). Occult filariasis (tropical pulmonary eosinophilia) is a clinical variant of *W. bancrofti* infection. Individual treatment with diethylcarbamazine which has both microfilaricidal and macrofilaricidal activity is effective. Total cumulative dosages of 72 mg/kg are generally recommended for *Wuchereria bancrofti* infections with half this dose used for *Brugia malayi* and *B. timori* infections. In all cases treatment is best initiated with smaller doses for 2-3 days to avoid the danger of immunological reactions. Rigorous hygiene to the affected limbs with adjunctive measures to minimize infection and promote lymph flow is important for reducing acute episodes of inflammation.

In communities where filariasis is endemic, annual administration of single doses of albendazole 400 mg with either diethylcarbamazine (6 mg/kg) or ivermectin (200 µg/kg) is effective for interrupting transmission; this treatment is continued for at least 5 years. Trials in India and China have shown that the consistent use for 6-12 months of table salt containing diethylcarbamazine 0.1% can eliminate *W. bancrofti*; a concentration of 0.3% for 3-4 months may be required where *B. malayi* is endemic.

Diethylcarbamazine*

Indications *Treatment of loiasis; prophylaxis of loiasis in temporary residents in endemic areas; tissue nematode infections; lymphatic filariasis; toxocariasis.*

Availability **TABLETS** 50 and 100 mg; **SYRUP** 5 mg/ml and 120 mg/5 ml.

Dose ***Oral***

Adult and child- 11 mg/kg body weight daily in three divided doses on the first day. Thereafter increase gradually to 6 mg/kg body weight given after food daily for two to three days. Hookworm infection: treat for 21 days. Filariasis: 2 mg/kg body weight is given three times a day for 3 to 4 weeks. 1 mg/kg body weight for an adult of 50 kg. Treatment may be repeated once after 6 months.

Contraindications Pregnancy (delay treatment until after delivery); infants, elderly, debilitated (usually excluded from mass treatment programmes; see also Precautions); cardiac disease, hypersensitivity, impaired renal function.

Precautions Renal impairment; cardiac disorders; other severe acute diseases-delay diethylcarbamazine treatment until after recovery; risk of meningoencephalitis in severe infection (see notes above).

Adverse Effects Headache, dizziness, drowsiness, nausea and vomiting; immunological reactions, within a few hour of the first dose, subsiding by fifth day of treatment and including fever, headache, joint pain, dizziness, anorexia, malaise, nausea and vomiting, urticaria and asthma in asthmatics (similar to Mazzotti reaction), induced by disintegrating microfilariae; microencephalitis (with heavy microfilaraemia, see notes above); reversible proteinuria; enlargement of lymph nodes.

Storage Store protected from moisture.

Ivermectin

Pregnancy Category-C

Indications *Nematodal infections such as ascariasis, trichuriasis, strongyloidiasis, enterbiasis, lymphatic filariasis, scabies and pediculosis.*

Availability **TABLETS** 3, 6, 9 and 12 mg; **INJECTION** 10 ml (0.1% w/v).

Dose	***Oral*** **Strongyloidiosis:** 200 µg/kg of body weight once daily for 1-2 days. **Lymphatic filariasis:** 400 µg/kg of body weight simple annual dose for 4-6 years. **Scabies and pediculosis:** 150-200 µg/kg of body weight single oral dose highly effective. Second dose may be required 7-10 days later.
Contraindications	Hypersensitivity, CNS disorders, pregnancy, meningitis, trypanosomiasis, seizures, contraindicated to children below the age of < 5 years old or under 15 kg body weight.
Precautions	Concurrent Loa Loa infection, impaired blood-brain barrier function, pregnancy (Appendix 7c), lactation, hepatic, cardiovascular, renal or pulmonary disease, anaemia, coagulation disorder, severe asthma, interactions (Appendix 6c).
Adverse Effects	Nausea, vomiting, constipation, abdominal pain and fatigue, rash, arthralgia, fever, myalgia, asthenia, hypotension, tachycardia, edema, lymphadenopathy, sore throat, cough, headache, somnolence, transient eosinophilia, dizziness, diarrhoea, pruritus, orthostatic hypotension, lymph-node tenderness, rare but serious adverse effects such as marked disability and encephalopathies in patients coinfected with heavy burdens of Loa microfilaria.

9.4 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.

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 5-fluorouracil by cytosine deaminase. Flucytosine is myelosuppressive and plasma concentrations above 75 µg/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, footware 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.

Potassium iodide aqueous oral solution is a clear liquid with a characteristic, strong salty taste. It is effective against sporotrichosis and subcutaneous phycomycosis, which are fungal infections caused by *Sporothrix schenckii* and *Basidiobolus haptosporus* respectively. In subcutaneous sporotrichosis, amphotericin B is often effective in patients unable to tolerate iodides. Itraconazole, by mouth has been tried as an alternative to potassium iodide in both cutaneous and extracutaneous sporotrichosis. In phycomycosis, fluconazole may be effective.

Amphotericin B*

Pregnancy Category-B

Schedule H

Indications	*Life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptaococcosis, mucormycosis, sporotrichosis and candidiasis; visceral and mucocutaneous leishmaniasis unresponsive to pentavalent antimony compounds; severe meningitis, perioral candidiasis.*
Availability	**VIALS** 10, 25, 50 and 100 mg plain, 50 mg/vial (liposomal).
Dose	***Intravenous infusion (plain)***

Adult- Systemic fungal infection: 250 µg/kg body weight daily, increase gradually 1 mg/kg body weight if tolerated (max 1.5 mg/kg body weight daily) or alternate days.

Child- Same as for Adult based on body weight.

Intravenous (liposomal)

For fever in neutropenic patients: 3 mg/kg/day, max. dose 5 mg/kg/day i.v.

For cryptococcal meningitis: 3-4 mg/kg, max. 6 mg/kg, i.v. once daily.

Visceral leismaniasis:
Immunocompetent patients: 3 mg/kg.

Immunocompromized patients: 4 mg/kg.

Contraindications

Toxic effects must be weighed against benefits. Regular kidney, liver function tests and blood counts must be conducted; lactation; antineoplastic therapy.

Precautions

Close medical supervision throughout treatment and initial test dose required (see note, below); renal impairment (Appendix 7d); pregnancy (Appendix 7c); hepatic and renal function tests; blood counts and plasma electrolyte monitoring; corticosteroids (avoid, except to control reactions); lactation; avoid rapid infusion (risk of arrhythmias); interactions (Appendix 6c); geriatric use.

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 min after the test dose.

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; respiratory failure.

Storage

Store in a tightly closed container between 2 to 8°C, protected from light.

Clotrimazole*

Pregnancy Category-B

Schedule H

Indications — *Vulvo-vaginal candidiasis, trichomoniasis, vaginitis, non-specific vaginitis, mixed vaginal infection, Gram-positive and Gram-negative bacterial infection, infective leucorrhoeas; prevention of athletes foot and ringworm disease of skin folds.*

Availability — **PESSARIES/VAGINAL TABLETS** 100 and 200 mg; **CREAM** 1% w/w; **POWDER** 75g; **LOTION** 50 ml.

Dose — **Adult-** Pessaries/vaginal tablets: 100 mg pessary/vaginal tablet to be inserted into vagina at night before going to bed as deep as possible for consecutive 6 to 7 days or 200 mg for 3 consecutive night before going to bed or 500 mg single dose.

Child- Pessaries/vaginal tablets: not recommended. Cream: Rub on affected area 2 to 3 times by applying in thin layer and rubbing, continue for 14 days after healing.

Contraindications — Ophthalmic use; hypersensitivity.

Precautions — Avoid contact with eyes, pregnancy (Appendix 7c) and lactation.

Adverse Effects — Local irritation, burning sensation and itching, abnormal liver function, unpleasant mouth sensation.

Storage — Store protected from light and moisture. Do not crush pessaries.

Fluconazole*

Pregnancy Category-C

Schedule H

Indications — *Systemic mycosis including histoplasmosis, non-meningeal coccidioidomycosis, para-coccidioidomycosis and blastomycosis treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; oesophageal and oropharyngeal candidiasis, vaginal candidiasis and systemic candidiasis.*

Availability **TABLETS/CAPSULES** 50, 100, 150 and 200 mg; **EYE DROPS** 5 ml (0.3% w/v).

Dose **Adult-** Mucosal: 50 to 100 mg daily for 14 to 30 days. Vaginal: 150 mg as a single dose. Oral: systemic loading dose of 400 mg on first day and thereafter 200 to 400 mg once daily for at least 28 days.

Prophylaxis of fungal infection: 50 to 100 mg once daily.

Contraindications Sensitivity to primaquine; infants below 1 year of age; alcohol; coadministration of cisapride, terfenadine.

Precautions Renal impairment (Appendix 7d); lactation (Appendix 7b); monitor liver function-discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis; Appendix 7a); interactions: (Appendix 6b, 6c); pregnancy (Appendix 7c); immunocompromised patients.

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.

Storage Stor in an airtight container.

Flucytosine

Pregnancy Category-C

Schedule H

Indications *Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis; adjunct to amphotericin B in systemic candidiasis; septicemia, pulmonary infection.*

Availability **CAPSULE** 250 mg; **INFUSION** 2.5g in 250 ml.

Dose ***Oral***

Adult- 250 mg four times a day for not more than 7 days.

Intravenous infusion- over 20 to 40 min;

Adult and Child- 200 mg/kg body weight daily in four divided doses.

Contraindications Renal impairment; elderly; blood disorders, pregnancy (Appendix 7c); hypersensitivity.

Precautions Elderly; renal impairment; also the use with amphotericin B (both nephrotoxic); liver- and kidney function tests and blood counts required (weekly in renal impairment or in blood disorders); lactation (Appendix 7b); interactions (Appendix 6c); pregnancy (Appendix 7c).

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; cardiac arrest, myocardial toxicity, dyspnoea, azotemia, ataxia, hypoglycemia.

Storage Store protected from light.

Griseofulvin*

Pregnancy Category-C

Indications *Fungal infections of the skin, scalp, hair and nails where topical treatment has failed or is inappropriate; athlete's foot.*

Availability **TABLETS** 125, 250, 375 and 500 mg; **CAPSULES** 125 mg.

Dose ***Oral***

Adult- 500 mg once a day or in divided doses, in severe infections dose may be doubled. Reduce when response occurs. Administer with meals.

Child- Under 50 kg: 10 mg/kg body weight once daily or divided doses with meals.

Contraindications Severe liver disease (Appendix 7a); pregnancy (Appendix 7c) (avoid pregnancy during and for 1 month after treatment; men should not father children within 6 months of treatment; 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); lactation; interactions (Appendix 6a, 6b, 6c, 6d); avoid exposure to sunlight/ artificial light.

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

Adverse Effects Headache, nausea, vomiting, diarrhoea, rashes, dizziness, fatigue reported; dry mouth and angular stomatitis; leukopenia, agranulocytosis; proteinuria reported; photosensitivity; lupus erythematosus, toxic epidermal necrolysis, erythema multiforme; serum sickness, angioedema; peripheral neuropathy; confusion and impaired coordination.

Storage Store in a well closed container.

Ketoconazole

Pregnancy Category-C

Schedule H

Indications *Malassezia fulliculitis dermatophytosis and chronic conditions which cannot be treated topically; infections resistant to fluconazole; blastomycosis, candidiasis, chromomycosis.*

Availability **TABLETS** 200 mg; **CREAM** 2% and 5% w/w; **SOLUTION** 2%w/v; **LOTION** 2%w/v.

Dose **Adult-** 200 to 400 mg daily once preferably after food.

Child- (Over 2 years) 3.3 to 6.6 mg/kg body weight once daily after food.

Local application- 3 to 4 times daily, apply thoroughly.

Contraindications Hepatic impairment; lactation; concomitant use with cisapride.

Precautions Predisposition to adrenocortical insufficiency; avoid in porphyria; pregnancy (Appendix 7c); interactions (Appendix 6a, 6c), hepatotoxicity

Potentially life-threatening hepatotoxicity reported very rarely,; risk of hepatotoxicity greater if given for longer than 14 days. Monitor liver function before treatment, then on weeks 2 and 4 of treatment, then every month. Avoid or use with caution if abnormal liver function tests (avoid in active liver disease) or if history of hepatotoxicity with other drugs.

Adverse Effects

Nausea, vomiting, abdominal pain; pruritus; less commonly diarrhoea, headache, dizziness, drowsiness and rash; very rarely, fatal liver damage (see Hepatotoxicity above), dyspepsia, raised intracranial pressure, adrenocortical insufficiency, erectile dysfunction, menstrual disorders, azoospermia (with high doses), gynaecomastia, thrombocytopenia, photophobia and alopecia.

Nystatin*

Pregnancy Category-C

Schedule H

Indications

Oral, oesophageal, intestinal, vaginal and cutaneous candidiasis.

Availability

TABLETS 5,00,000 units; **OINTMENT** 3g (100000 IU).

Dose

Oral

Adult- Intestinal candidiasis: 5,00,000 units every six h, doubled in severe infections.

Child- 1 month to 12 years: 1,00,000 units 4 times daily, immunocompromised children may require higher doses up to 5,00,000 units.

Topical application

Dissolve one tablet in glycerine and apply locally 3 to 4 times.

Intravaginal

Insert one tablet deep into vagina before bed time once at night.

Contraindications

Hypersensitivity.

Precautions Lactation; discontinue if sensitivity develops, teratogenic effect, should not be used for the treatment of systemic, oral, intravaginal or ophthalmic infections; preganacy (Appendix 7c).

Adverse Effects Nausea, vomiting, diarrhoea at high doses; oral irritation and sensitization; rash and rarely, erythema multiforme (Steven's-Johnson syndrome); eczema, burning.

Storage Store protected from light and moisture.

Tolnaftate

Pregnancy Category-C

Indications *Ringworm infections, athlete's foot.*

Availability **CREAM** 10% w/w.; **OINTMENT-** 10 % w/w. **SOLUTION-** 10% w/v.

Dose Rub sufficient quantity gently into affected area 2-3 times daily.

Contraindications Hypersensitivity, deep infections.

Precautions Avoid contact with eyes and mucous membranes; mixed infections. Discontinue if irritation occurs on application, pregnancy (Appendix 7c).

Adverse Effects Stinging, irritation, sensitization.

9.5 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.

1. Diphyllobothriasis:

In diphyllobothriasis, niclosamide or praziquantel in a single dose is highly effective. Hydroxocobalamin and folic acid supplements may also be required.

2. 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 mebendazole and 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.

3. Hymenolepiasis:

In hymenolepiasis, praziquantel is more effective than niclosamide, although resistance to praziquantel has been reported. Repeated treatment may be necessary to cure intense infections or to eliminate the parasite within a family group or institution.

4. Taeniasis:

In taeniasis, praziquantel is well tolerated and extensively absorbed and kills adult intestinal taenia worms in a single

dose. Praziquantel also kills *T. solium* cysticerci when taken for 14 days in high doses. It thus offers the prospect of a cure for neurocysticercosis, which has been treatable only by surgery, anti-inflammatory corticosteroids and anticonvulsants. However, because dying and disintegrating cysts may induce localized cerebral oedema, treatment with praziquantel must always be undertaken in a hospital setting. In addition, a corticosteroid is usually given to reduce the inflammatory response. Albendazole also kills neurocysticerci when given daily for one month; a corticosteroid or an antihistamine is also given to reduce any inflammatory reaction. The longer-established niclosamide acts only against the adult intestinal worms. Cestode infections due to *T. solium,* occurring during pregnancy should always be treated immediately (with praziquantel or niclosamide, but not with albendazole) because of the risk of cysticercosis.

Intestinal Nematode Infections:

Intestinal nematode infections include ascariasis, capillariasis, enterobiasis, hookworm infection, strongyloidiasis, trichostrongyliasis and trichuriasis.

1. Ascariasis:

Ascariasis is an infection, usually of the small intestine, caused by Ascaris *lumbricoides* (roundworm). Single doses of levamisole or pyrantel are effective; the broad-spectrum anthelmintics, albendazole or mebendazole are also effective.

2. Capillariasis:

Capillariasis is caused by infection of the intestine with *Capillaria philippinensis*. Prolonged treatment with mebendazole or albendazole offers the only prospect of cure.

3. 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.

4. 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.

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 sulphate (200 mg daily for adults) for at least 3 months after the haemoglobin concentration of 12g/100 ml is obtained.

5. 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 µg/kg or 200 µg/kg/day on two consecutive days is the treatment 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.

6. Trichostrongyliasis:

Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp. In symptomatic trichostrongyliasis, a single dose of pyrantel (10 mg/kg) or albendazole (400 mg) is effective.

7. Trichuriasis:

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; severe infec-

tions require a 3-day course.

Tissue Nematode Infections:

Tissue nematode infections include angiostrongyliasis, anisakiasis, cutaneous larva migrans, dracunculiasis, trichinellosis and visceral larva migrans.

1. Angiostrongyliasis:

Angiostrongyliasis is caused by infection with the larvae of the rat lungworm, *Parastrongylus cantonensis* (*Angiostrongylus cantonensis*). Symptomatic treatment pending spontaneous recovery is often all that is required.

2. Anisakiasis:

Anisakiasis is caused by infection with seafood containing larvae of *Anisakis, Contracaecum* or *Pseudoterranova* spp. In anisakiasis, anthelminthic treatment is rarely, necessary. Prevention is dependent upon informing communities of the hazards of eating raw or inadequately prepared salt-water fish; and early evisceration of fish after capture and freezing of seafood at -20^{o}C for at least 60 h before sale.

3. Cutaneous Larva Migrans:

Cutaneous larva migrans (creeping eruption) is caused by infection with larvae of animal hookworms, usually *Ancylostoma braziliense* and *A. caninum* which infect cats and dogs. Albendazole in a single dose of 400 mg is effective.

4. Dracunculiasis:

Dracunculiasis (dracontiasis, guinea-worm infection) is caused by infection with *Dracunculus medinensis*, acquired through drinking water containing larvae that develop in small freshwater crustaceans. Metronidazole (25 mg/kg daily for 10 days, with a daily max. of 750 mg for children) provides rapid symptomatic relief. It also weakens the anchorage of the worms in the subcutaneous tissues and they can then be removed by traction. However, since it has no effect on the larvae of pre-emergent worms, it does not immediately prevent transmission.

5. Trichinellosis:

Trichinellosis (trichinosis) is caused by infection with the larvae of *Trichinella spiralis*. Each case of confirmed or even suspected trichinellosis infection should be treated in order to prevent the continued production of larvae. In both adults and children, mebendazole (200 mg daily for 5 days), albendazole (400 mg daily for 3 days) and pyrantel (10 mg/kg daily for 5 days) are all effective. Prednisolone (40-60 mg daily) may be needed to alleviate the allergic and inflammatory symptoms.

6. Visceral Larva Migrans:

Visceral larva migrans (toxocariasis) is caused by infection with the larval forms of *Toxocara canis* and less commonly, *T. cati* (which infect dogs and cats). Treatment should be reserved for symptomatic infections. A 3 week oral course of diethylcarbamazine kills the larvae and arrests the disease, but established lesions are irreversible. To reduce the intensity of allergic reactions induced by dying larvae, dosage is commonly commenced at 1 mg/kg twice daily and raised progressively to 3 mg/kg twice daily (adults and children).

Ocular larva migrans occurs when larvae invade the eye, causing a granuloma which may result in blindness. In order to suppress allergic inflammatory responses in patients with ophthalmic lesions, prednisolone should be administered concurrently, either topically or systemically.

Albendazole*

Pregnancy Category-C

Schedule H

Indications

Echinococcus multilocularis and E. granulosus infections prior to or not amenable to surgery; neurocysticercosis; nematode infections; filariasis; ascariasis, hookworm infections, strongyloidiasis, enterobiasis, trichuriasis, trichostrongyliasis and capillariasis; cestode infections; tissue nematode infections.

Availability

CHEWABLE/PLAIN TABLET 150, 200, 400 mg & 1.5g; **CAPSULE** 400 mg; **ORAL SUSPENSION** 200 mg/5 ml; **SYRUP** 200 mg/5 ml; **DROPS** 10 ml (200 mg/ml)

Dose

Oral

Adult and child above 2 years- 400 mg daily as a single dose.

Strongyloidiasis, taeniasis and H. nana infection: 400 mg once daily is given for 3 consecutive days. Hydatid disease: 400 mg twice daily with meals for 28 days (therapy may be repeated after 14 days in three cycles).

Child- 1 to 2 years: 200 mg as a single dose.

Contraindications

Pregnancy, adequate measures must be taken for non-hormonal contraceptive during and one month after therapy; hypersensitivity.

Precautions

Pregnancy (see notes above and Appendix 7c); liver impairment, increased intracranial pressure; seizures; monitor blood count and liver function.

Adverse Effects Gastrointestinal discomfort; headache; adverse effects associated with use in cestode infections; reversible alopecia; leucopenia, neurocystecercosis; Steven's Johnson syndrome.

Storage Store protected from light.

Mebendazole

Pregnancy Category-C

Schedule H

Indications *Echinococcus granulosus and E. multilocularis infections before surgery or not amenable to surgery; nematode infections.*

Availability **TABLET** 100 mg; **ORAL SUSPENSION** 100 mg/5 ml.

Dose ***Oral***

Adult and child over 2 years- Threadworm infection: 100 mg single dose. If re-infection occurs second dose may be needed after 2 weeks. Whip worm, roundworm and hookworm infection: 100 mg twice daily for 3 days.

Contraindications Pregnancy; lactation; hypersensitivity; patients with CNS disorders.

Precautions Pregnancy (Appendix 7c; see also notes above); lactation; interactions (Appendix 6c, 6d); expulsion of ascaris from mouth or nose; monitor blood count or hepatic function.

Adverse Effects Gastrointestinal disturbances; headache and dizziness; adverse effects associated with use in cestode infections; abdominal pain, diarrhoea; rashes, urticaria, angioedema.

Storage Store protected from light and moisture.

Niclosamide

Pregnancy Category-B

Schedule H

Indications *Taenia saginata, T. solium, Hymenolepis nana and Diphyllobothrium latum infections.*

Availability **TABLETS** 500 mg and 1g.

Dose ***Oral***

Adult- 1g (2 tablets) chewed and swallowed with water on empty stomach. Followed by another dose of 1g one h later. Brisk purgative after 2 h of last dose is recommended.

H. nana infection: 2g daily after food on first day thereafter 1g for next 6 days.

Contraindications Hypersensitivity; purgative must be given after two h to clear bowel since ova in dead segments are not cleared without purgative. Infection may recur if purgative is not given.

Precautions Chronic constipation (restore regular bowel movement before treatment); give antiemetic before treatment; not effective against larval worms; pregnancy (Appendix 7c).

Adverse Effects Nausea; retching; abdominal pain; lightheadedness; pruritus; anorexia, emesis, perianal itching.

Storage Store protected from light and moisture.

Pyrantel Pamoate

Pregnancy Category-C

Schedule H

Indications *Ascariasis; hookworm infections; enterobiasis; trichostrongyliasis; tissue nematode infection.*

Availability **TABLET** 250 mg;
ORAL SUSPENSION 250 mg/ml.

Dose ***Oral***

11 mg/kg (max 1g) in a single dose (given for 2 consecutive days in case of heavy hookworm infestation).

Contraindications Hepatic diseases.

Precautions Pregnancy (Appendix 7c; lactation; liver disease (reduce dose); severe malnutrition, anaemia, concurrent administration with piperazine.

Adverse Effects Mild gastrointestinal disturbances; headache; dizziness; drowsiness; insomnia; rash and elevated liver enzymes.

Storage Store protected from light at temperature not exceeding 30°C.

9.6 Anti-Leishmaniasis 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, meglumine antimoniate or 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. However, biopsies should be repeated after 3 and 12 months since relapse is frequent. Antimonials combined with allopurinol, pentamidine isothionate and amphotericin B have been used with success in patients in relapse who have become unresponsive to antimonials alone.

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 isothionate, 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 isothionate may be needed until clinical immunity is established.

Miltefosine

Pregnancy Category-X

Schedule H

Indications	*As directly observed therapy (DOT) of visceral Leishmaniasis caused by Leishmania donovani.*
Availability	**CAPSULES** 10 mg, 50 mg
Dose	***Oral*** **Adult- (>12 years): Weighing >25 kg:** 100 mg/day, twice a day, after meals for 28 days. **<25 kg:** 50 mg/day, after meals for 28 days **Child (2-11 years):** 2.5 mg/kg daily after meals for 28 days, i.e., 50 mg once daily.
Contraindications	Children below 2 years, patients with HIV, newborns, pregnancy (Appendix 7C) and lactation.

Precautions Avoid contact with eyes, kidney or liver impairment, may impair ability to drive or operate machinery.

Adverse Effects Nausea and vomiting, GI irritation, diarrhoea, constipation, ocular, hepatic, renal toxicity, skin rash, leukocytosis, thrombocytosis

Storage Store in a cool place, protected from light and moisture.

Pentamidine*

Pregnancy Category-C

Schedule H

Indications *Leishmaniasis; African trypanosomiasis; Pneumocystis carinii pneumonia.*

Availability **INJECTION** 200 and 300 mg Vials.

Dose ***Deep intramuscular injection.***

3 to 4 mg/kg body weight on alternate days to a max. of 10 injection. Course may be repeated if necessary.

Contraindications Severe renal impairment.

Precautions Risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down); monitor blood pressure during administration and treatment period; hypertension; hypoglycaemia or hyperglycaemia; hepatic impairment; leukopenia, thrombocytopenia, anaemia; immunodeficiency-if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment; renal impairment; pregnancy-in potentially fatal visceral leishmaniasis, pregnancy (Appendix 7c); lactation (Appendix 7b); history of asthma.

Adverse Effects Nephrotoxicity; acute hypotension-with dizziness, headache, breathlessness; tachycardia and syncope following rapid intravenous injection; hypoglycaemia-may be followed by hyperglycaemia and type I diabetes mellitus; pancreatitis; also hypocalcaemia, gastrointestinal disturbances; confusion, hallucinations; arrhythmias; thrombocytopenia, leukopenia, abnormal liver function tests; hyperkalaemia; rash, Stevens-Johnson syndrome, reported; pain, local induration, sterile abscess and muscle necrosis at injection site; night sweat, diarrhoea, nausea, anaemia, wheezing, bad taste, anxiety, insomnia, miscarriage, erythema.

Storage Store protected from moisture in a single dose container.

Sodium Stibogluconate*

Indications

Leishmaniasis/Kala-azar.

Availability

INJECTION vial 30 ml (0.33g equivalent to total antimony 100 mg/ml).

Dose

4 to 6g for full course.

Slow intravenous infusion

20 mg/kg/day.

Contraindications

Severe kidney disorders; lactation.

Precautions

Provide protein-rich diet throughout treatment and, if possible, correct iron and other nutritional deficiencies; renal and hepatic impairment; 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 min (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); treat intercurrent infection (for example pneumonia); lactation; ECG monitoring.

Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be life-threatening if pharyngeal or tracheal involvement)-may require corticosteroids.

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; phlebotoxicity, metallic taste in mouth, dizziness.

Storage

Store protected from moisture.

9.7 Antimalarial Drugs

Human malaria, which is transmitted by female 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:

Blood schizonticides, 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 (example amodiaquine and chloroquine), the related arylaminoalcohols (example mefloquine and quinine) and artemisinin and its derivatives (example artemether and artesunate). Blood schizonticides 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 combination. For example, pyrimethamine in combination with a sulfonamide (sulfadoxine) or sulfone and some antibiotics (for example doxycycline) are blood schizonticides. 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 schizonticide, 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.

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 artesunate. 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. Because sulfonamides are associated with a risk of haemolysis and methaemoglobinaemia in the newborn, quinine is preferred to treat chloroquine-resistant malaria during pregnancy.

Mefloquine 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. Doxycycline, which is an effective oral schizonticide, 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 multi-drug resistant falciparum malaria oral artesunate may be an effective antimalarial. It should always be given in combination with mefloquine. Parenteral artemether or artesunate, 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 artesunate, 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 lactation.

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 schizonticide with little blood schizonticidal 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 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 vulnerablility 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.

9.7.1 Drugs for Prophylaxis

Chloroquine* (Refer Page No. 383)

Pregnancy Category-D

Indications

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.

Availability

TABLETS 250 and 500 mg; **INJECTION** 10 and 30 ml (40 mg/ml); **SUSPENSION** 50 mg/ml.

Dose

Oral

Adult- Immediately 600 mg, after 6 h 300 mg followed by 300 mg daily for 2 days.

Child- 10 mg/kg body weight followed by 5 mg/kg body weight after 6 h, thereafter once a day for 2 days.

Intramuscular injection

Adult- 10 ml followed by 5 ml after 6 h. Thereafter 5 ml daily for two days.

Child- 5 mg/kg body weight administered every 12 h followed by oral therapy.

Contraindications

Severe haematologic distress or gastrointestinal distress; eye dysfunction; liver disease.

Precautions

If patient continues to deteriorate after chloroquine-suspect resistance and administer quinine intravenously as emergency measure; hepatic impairment; renal impairment (Appendix 7d); pregnancy (but in malaria, benefit considered to outweigh risk; Appendix 7c); lactation (Appendix 7b); may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of epilepsy); may aggravate myasthenia gravis; severe gastrointestinal disorders; G-6-PD deficiency; avoid concurrent therapy with hepatotoxic drugs; interactions (Appendix 6c, 6d).

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.

Storage Store protected from light.

Doxycycline* (Refer Page No. 134)

Pregnancy Category-D

Schedule H

Indications *Supplement to quinine in treatment of multiple-medicine resistant P. falciparum malaria (where quinine resistance, in cases of hypersensitivity to sulfonamides); short-term prophylaxis of multiple-medicine resistant P. falciparum malaria; bacterial infections.*

Availability **CAPSULES/TABLETS** 50, 100, 150 and 200 mg; **SYRUP** 25 mg/5 ml.

Dose ***Oral***

Adult- 200 mg on the first day then 100 mg daily.

Severe infections including refractory urinary tract infection: 200 mg daily can be used.

Early syphilis: 100 mg twice daily for 14 days and for latent syphilis 200 mg twice daily for 28 days is used.

Uncomplicated genital Chlamydia, non-gonococcal urethritis: 100 mg twice daily for 7 days.

Child- Only if alternate antibacterial cannot be given 5 mg/kg body weight in two divided doses.

Contraindications Pregnancy (Appendix 7c); children under 8 years; porphyria; systemic lupus erythematosus; prolonged exposure to sunlight, severe hepatic dysfunction.

Precautions Avoid exposure to sunlight or sunlamps-photosensitivity reported; renal impairment; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6c).

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; nasopharyngitis, reduced tibular growth rate, diarrhoea, sinusitis.

Storage Store protected from light and moisture at a temperature not exceeding 30°C.

Primaquine*

Indications *Radical cure of P. vivax and P. ovale malaria (after chloroquine therapy to eradicate erythrocytic forms), elimination of gametocytes of P. Falciparum, malaria prophylaxis.*

Availability **TABLETS** 2.5, 7.5 and 15 mg.

Dose ***Radical treatment***

Adult- 15 mg daily for 14 days, may be increased to higher dose.

Child- 250 µg/kg daily for 14 days.

Malaria prophylaxis

Adult- 30 mg once daily; **Child-** 0.5 mg/kg once daily (to be started 1-2 days before travel and continue for 7 days after departure from malaria endemic area).

Gametocidal treatment of *P. falciparum* malaria (after standard blood schizontocide therapy).

Adult and Child- 500–50 µg/kg as a single dose.

Contraindications Hypersensitivity, granulocytopenia, pregnancy, lactation, children below 1 year.

Precautions Patients with history of granulocytosis/ methaemoglobinaemia, G-6-PD deficiency, monitor Hb levels, blood counts routinely and withdraw if signs of haemolysis or methaemoglobinaemia occur; lactation (Appendix7b).

Adverse effects Nausea, vomiting, abdominal cramps, haemolytic anaemia in G-6-PD deficient patients; rarely, leukopenia, agranulocytosis, leukocytosis, methaemoglobinaemia and cardiac arrythmias.

Storage Store protected from moisture.

Proguanil

Pregnancy Category-B

Schedule H

Indications *With chloroquine, prophylaxis of malaria in areas of low resistance.*

Availability **TABLET** 100 mg.

Dose ***Oral***

Prophylaxis

Adult- Preferably 200 mg once daily, start 1 to 2 days before entering endemic area and continue for 4 weeks after leaving.

Child- (11-20 kg) - 25 mg once daily;
(21-30 kg)- 50 mg once daily;
(31-40 kg)- 75 mg once daily;
more than 40 kg- 100 mg once daily.

Treatment

Adult and child- over 40 kg; 100 mg once daily.

Child- Up to 1 year: 25 mg; 1 to 4 years; 50 mg; 5 to 8 years: 100 mg; 9 to 14 years: 150 mg; above 14 years: 200 mg.

Contraindications Use in areas of known resistance to either proguanil or pyrimethamine.

Precautions Renal impairment; pregnancy (folate supplements required, Appendix 7c); lactation.

Adverse Effects Mild gastric intolerance, diarrhoea; occasional mouth ulcers and stomatitis; skin reactions and hair loss reported; rarely, hypersensitivity reactions such as urticaria and angioedema.

Storage Store protected from light and moisture.

9.7.2 Drugs for Curative Treatment

Amodiaquine

Schedule H

Indications — *Treatment of uncomplicated malaria caused by P. falciparum.*

Availability — **TABLET** 200 mg; **SUSPENSION** 50 mg/5 ml.

Dose — ***Oral***

Adult- Prophylaxis: 300 mg once weekly, start one week before entering endemic area and continue for 4 weeks after leaving.

Infant- up to 12 weeks, body weight under 6 kg: 37.5 mg once weekly,
1 year body weight 6 to 10 kg: 75 mg once weekly.

Child- 1 to 4 years, body weight 10 to 16 kg: 11 to 12.5 mg once weekly.
4 to 8 years: body weight
16 to 25 kg: 150 mg once a week.
8 to 13 years, body weight over 45 kg: adult dose is used.

Contraindications — Hepatic impairment (Appendix 7a); blood disorders, retinopathy.

Precautions — Pregnancy and lactation; G-6-PD deficiency; avoid concurrent therapy with hepatotoxic drugs.

Patients and their caretakers should be told how to recognize the signs of blood disorders and advised to seek medical attention as soon as possible if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. They should also be told how to recognize signs of hepatitis and advised to seek medical attention if symptoms such as anorexia, abnormal weight loss, asthenia, abdominal pains, fever, nausea or vomiting develop.

Adverse Effects — Blood disorders including leukopenia and agranulocytosis; hepatitis; gastrointestinal disturbances, visual disturbances (retinopathy associated with long-term, high-dose therapy); rarely, rash, pruritus, skin pigmentation, neuromyopathy.

Arteether

Pregnancy Category-C

Schedule H

Indications — *Complicated falciparum malaria; chloroquine resistant malaria; cerebral malaria.*

Availability — **INJECTION** 2 ml ampoule (150 mg/2 ml).

(Arteether is an ethyl derivative of dihydro-artimisinin. It is a mixture of α and β arteether in a 30:70 ratio)

Dose **Adult-** 150 mg daily i.m. injection, once daily for 3 consecutive days.

Contraindications Hypersensitivity to artemisinin derivatives; preganacy (Appendix 7c).

Adverse reactions It is clinically very well tolerated without any significant side effects; neurological or biochemical.

Storage Store protected from light in tamper evident container so as to avoid contamination by micro-organisms.

Artemether

Pregnancy Category-C

Schedule H

Indications *Treatment of severe P. falciparum malaria in areas where evidence is there that quinine is ineffective; multi drug resistant malaria.*

Availability **CAPSULE** 40 mg; I**NJECTION** 1 ml ampoule (80 mg/ml, 160 mg/2 ml).

Dose ***Oral***

Adult- 160 mg in two divided doses on first day followed by 80 mg once a day for next four days.

Intramuscular injection

Adult- 80 mg twice a day for 3 days.

Child- 1.6 mg/kg body weight twice a day followed by 1.6 mg/kg body weight once a day for 4 days, alternatively 1.6 mg/kg body weight twice a day for 3 days.

Contraindications First trimester of pregnancy (Appendix 7c); hypersensitivity.

Precautions Electrolyte disturbances, concomitant use with other drugs known to cause QT-interval prolongation; hepatic impairment; renal impairment; monitor patients unable to take food (greater risk of recrudescence); interactions (Appendix 6c); lactation (Appendix 7b).

Dizziness may impair ability to perform skilled tasks, for example operating machinery, driving.

Adverse Effects Headache, nausea, vomiting, abdominal pain, diarrhoea; dizziness, tinnitus, neutropenia, elevated liver enzyme values; cardiotoxicity (after high doses); neurotoxicity-in animal studies; decrease in reticulicyte count.

Storage Store protected from light and moisture.

Artesunate*

Pregnancy Category-C

Schedule H

Indications *Treatment of uncomplicated P. falciparum malaria in areas of multiple drug resistance.*

Availability **TABLET** 25, 50 & 60 mg; **INJECTION** 50, 60, 1000 & 2000 mg/vial.

Dose ***Oral***

Adult- total oral dose 600 mg can be divided into two 50 mg tablets twice a day on first day thereafter 50 mg twice a day for next 4 days.

Child- half adult dose.

Intramuscular injection

60 mg twice daily.

Contraindications First trimester of pregnancy (Appendix 7c); hypersensitivity.

Precautions Risk of recurrence if used alone in non-immune patients; hepatic/renal insufficiency, pregnancy (Appendix 7c), lactation, paediatrics.

Dizziness may impair ability to perform skilled tasks, for example operating machinery, driving.

Adverse Effects Headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus, neutropenia, elevated liver enzyme values; ECG abnormalities, including prolongation of QT interval; temporary suppression of reticulocyte response and induction of blackwater fever reported; neurotoxicity-in animal studies.

Storage Store protected from light and moisture.

Chloroquine* (Refer Page No. 178 and 383)

Doxycycline* (Refer Page No. 134 and 179)

Quinine*

Pregnancy Category-X

Indications *Multiple drug resistant P. falciparum malaria.*

Availability **TABLETS** 100, 150, 300 and 600 mg; **SUSPENSION** 150 mg/5 ml; **INJECTION** 1 and 2 ml ampoule (300 mg/ml).

Dose ***Oral***

Adult- 300 to 600 mg every 8 h in divided doses for 5 to 7 days.

Child- 25 mg/kg body weight every 8 h in divided doses for 5 to 7days.

Intravenous infusion for patients unable to swallow tablets

Loading dose 900 mg to 1.4g infused over 4 h, then 300 to 600 mg every 8 h infused over 4 h.

Contraindications Haemoglobinuria; optic neuritis; tinnitus; quinine resistant falciparum, pregnancy (Appendix 7c), lactation, prolonged QT interval.

Precautions Atrial fibrillation, conduction defects, heart block; monitor for signs of cardiac toxicity and blood glucose levels (with intravenous use); renal impairment (Appendix 7d); G-6-PD deficiency; may aggravate myasthenia gravis; interactions (Appendix 6d).

Adverse Effects Cinchonism (tinnitus, headache, blurred vision, temporary blindness, altered auditory acuity, nausea, diarrhoea, hot and flushed skin, rashes, confusion); hypersensitivity reactions including angioedema; rarely, haemorrhage and asthma; hypoglycaemia (especially after parenteral administration); renal damage (culminating in acute renal failure and anuria); blood disorders; cardiovascular, gastrointestinal and CNS effects; very toxic in overdosage-immediate medical attention required; acute haemolytic anaemia.

Storage Store protected from light.

Sulfadoxine + Pyrimethamine*

Pregnancy Category-C

Schedule H

Indications *Treatment of malaria due to susceptible P. falciparum in areas of high chloroquine resistance and in patients who have not responded to chloroquine; additionally quinine may be given for 3 days.*

Availability

TABLETS Sulfadoxine 500 mg + Pyrimethamine 25 mg; **SUSPENSION** 5 ml (500 mg sulfadoxine+25 mg pyrimethamine).

Dose

Oral

Adult- Prophylaxis: one tablet once a week. Treatment: 2 tablets in single dose.

Child- Under 4 years: half a tablet.
4 to 8 years: one tablet.
9 to 14 years: two tablets single dose.

Prophylaxis: Under 4 years 1/4th tablet.
4 to 8 years: half tablet.
9 to 14 years: 3/4th tablet once a week.

Contraindications

Hypersensitivity to sulfonamides or pyrimethamine; severe hepatic or renal impairment (except where no alternative treatment available); blood dyscrasias, neonates, megaloblastic anaemia and folate deficiency.

Precautions

Avoid in blood disorders-unless specialist supervision; discontinue immediately if blood disorder occurs; rash, sore throat, mouth ulcers, or shortness of breath-withdraw treatment; G-6-PD deficiency; predisposition to folate deficiency; hepatic impairment (Appendix 7a); pregnancy (Appendix 7c); lactation (Appendix 7b); interactions (Appendix 6c).

Adverse Effects

Rashes, pruritus, slight hair loss; rarely, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; gastrointestinal disturbances including nausea, vomiting, stomatitis; rarely, hepatitis, leukopenia, thrombocytopenia, megaloblastic anaemia and purpura-withdraw treatment; fatigue, headache, fever, polyneuritis, also reported; pulmonary infiltrates such as eosinophilic or allergic alveolitis-if symptoms of cough or shortness of breath-withdraw treatment.

Storage

Store protected from light and moisture.

9.8 Antimycobacterial Drugs

9.8.1 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).

Drugs 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 reactions 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 dose 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 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

Clofazimine*

Pregnancy Category-C

Schedule H

Indications *MB leprosy; type 2 lepra reactions.*

Availability **TABLETS** 25, 50, 100 mg; **CAPSULES** 50 and 100 mg.

Dose ***Oral***

Adult- 300 mg spread over a week. Sulfone resistant cases: 600 mg weekly preferably after meal.

Lepra reaction: 200 mg daily for 3 weeks or as required.

Child- 1 to 2 mg/kg body weight daily or 4 to 6 mg/kg body weight once a month.

Contraindications Pregnancy (Appendix 7c), lactation, renal and hepatic impairment.

Precautions Pre-existing gastrointestinal symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment); liver and renal impairment; may discolour soft contact lenses; paediatrics, elderly, interactions (Appendix 6d).

Adverse Effects Reversible discolouration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine; dose-related gastrointestinal symptoms including pain, nausea, vomiting and diarrhoea; severe mucosal and submucosal oedema, with prolonged treatment with high doses-may be severe enough to cause subacute small-bowel obstruction (see also Precautions); pruritus, ichthyosis, elevated blood sugar, diminished vision, dizziness, eosinophillic enteropathy.

Storage Store protected from moisture.

Dapsone*

Pregnancy Category-C

Schedule H

Indications *PB and MB leprosy; acne vulgaris, dermatitis, pneumocystic pneumonia.*

Availability **TABLETS** 25, 50 and 100 mg; **GEL** 5% w/w.

Dose ***Oral***

Adult- Leprosy: 50 to 100 mg daily depending upon body weight. Dermatitis herpetiformis: start with 50 mg daily and increase up to 400 mg till full response is obtained; dose reduced to minimum maintenance level as soon as possible.

Child- 1 to 2 mg/kg body weight as minimum dose to start with, increased weekly so that at the end of 7th week patient is receiving max. dose.

Contraindications Hypersensitivity to sulfones; severe anaemia; porphyria.

Precautions Anaemia (treat severe anaemia before therapy and monitor blood counts during treatment); susceptibility to haemolysis including G-6-PD deficiency (including lactation affected infants); lactation (Appendix 7b); porphyria; interactions (Appendix 6c); hyperbilirubinemia, methaemoglobinemia; renal impairment (Appendix 7d); pregnancy (Appendix 7c).

On long-term treatment patients and their caretakers should be told how to recognize blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

Adverse Effects Haemolysis and methaemoglobinaemia; allergic dermatitis (rarely, including toxic epidermal necrolysis and the Stevens-Johnson syndrome); rarely, hepatitis and agranulocytosis; 'dapsone syndrome' resembling mononucleosis-rare hypersensitivity reaction with symptoms including rash, fever, jaundice and eosinophilia; gastrointestinal irritation; tachycardia, headache, nervousness, insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy and psychoses reported; increase in reticulocytes, vertigo; pancreatitis; renal papillary necrosis; anorexia.

Storage Store protected from light.

Rifampicin* (Refer Page No. 200)

Pregnancy Category-C

Schedule H

Indications *PB leprosy; MB leprosy; tuberculosis.*

Availability **CAPSULES** 150, 300, 450 and 600 mg; **TABLETS** 150, 300, 350, 450, 500, 600 and 750 mg; **SYRUP** 100 mg/5 ml.

Dose

Oral

Adult- 450 to 600 mg single dose before breakfast.

Child- 10 to 20 mg/kg body weight daily.

Contraindications

Hypersensitivity; jaundice; patients with earlier drug induced liver disease.

Precautions

Reduce dose in hepatic impairment (Appendix 7a); 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); lactation; porphyria; discolours soft contact lenses; advise patients on oral contraceptives to use additional means; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).

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

Patients or their caretakers 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.

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-m ore frequent with intermittent therapy; alterations of liver function-jaundice and potentially fatal hepatitis (dose-related, do not exceed max. daily dose of 600 mg); 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; cerebral haemorrhage, visual disturbances.

Storage

Store protected from light and moisture.

9.8.2 Antituberculosis Drugs

Tuberculosis is a chronic infectious disease caused primarily by *Mycobacterium tuberculosis* or sometimes by *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 of dosage regimen 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, levofloxacin 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[1]

Drug	Initial phase (2 months)	Continuation phase (4 months)
Isoniazid	5 mg/kg daily	5 mg/kg daily
Rifampicin	10 mg/kg daily	10 mg/kg daily
Pyrazinamide	25 mg/kg daily	
together with		
Streptomycin[3]	15 mg/kg daily	
or		
Ethambutol[2]	15 mg/kg daily	
Isoniazid	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
Rifampicin	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
Pyrazinamide	35 mg/kg 3 times weekly	
together with		
Streptomycin[3]	15 mg/kg 3 times weekly	
or		
Ethambutol	30 mg/kg 3 times weekly	

[1]Unless otherwise indicated, doses are suitable for both adults and children

[2]Not suitable for children

Recommended 8-month treatment regimen for tuberculosis[1]

Drug Initial phase (2 months)	Continuation phase (6 months)
Isoniazid 5 mg/kg daily	5 mg/kg daily
Rifampicin 10 mg/kg daily	
Pyrazinamide 25 mg/kg daily	
together with	
Ethambutol[3] 15 mg/kg daily	15 mg/kg daily[4]
or	
Streptomycin[2] 15 mg/kg daily	

[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]Thiacetazone (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

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 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 re-treatment)[4]

specially designed standardized or individualized regimens recommended

Treatment regimens by category of tuberculosis diagnosis

[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

Amikacin*

Pregnancy Category-D

Schedule H

Indications *Short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including Pseudomonas species, Escherichia coli, species of indole-positive and indole-negative Proteus, Providencia species, Klebsiella, Enterobacter, Serratia species and Acinetobacter (Mima-Herellea) species.*

Availability **INJECTION** 10 ml vial (100 mg/2 ml), 2 ml vial (250 mg/2 ml), (500 mg/2 ml).

Dose ***Intramuscular or intravenous injection or infusion***

Adult- 15 mg/kg body weight daily in two divided doses, increased to 22.5 mg/kg body weight daily in three divided doses in severe infections. (max 1.5g daily for 10 days, max. cumulative dose is 15g).

Child- 15 mg/kg body weight daily in two divided doses.

Neonates- loading dose is 10 mg/kg body weight followed by 15 mg/kg body weight in two divided doses.

Contraindications Myasthenia gravis; hypersensitivity.

Precautions Pregnancy (Appendix 7c), renal impairment (Appendix 7d); neonates, infants and elderly; cross allergenicity.

Adverse Effects Vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis, stomatitis; also reported, nausea, vomiting, rash, blood disorders; acute muscular paralysis; albuminuria; azotemia.

Capreomycin

Pregnancy Category-C

Schedule H

Indications *Tuberculosis, in combination with other first line drugs for tuberculosis.*

Availability **INJECTION** 0.5, 0.75 and 1g/vial.

Dose ***Deep intramuscular injection***

Adult- 1g daily for 2 to 4 months (not more than 20 mg/kg body weight). Then 1 to 2g 2 to 3 times each week, in case of renal impairment reduce the dose in accordance with creatinine clearance.

Contraindications Not for paediatric use; hypersensitivity to capreomycin.

Precautions Renal impairment; hepatic impairment; auditory impairment; monitor renal, hepatic, auditory and vestibular function and electrolytes; pregnancy (teratogenic in animals; Appendix 7c) and lactation; interactions (Appendix 6c).

Adverse Effects Hypersensitivity reactions including urticaria and rashes; eosinophilia; leucocytosis or leucopenia, rarely, thrombocytopenia; changes in liver function tests; nephrotoxicity, electrolyte disturbances; hearing loss with tinnitus and vertigo; neuromuscular block after large doses, pain and induration at injection site.

Storage Store protected from moisture at a temperature not exceeding 25°C.

Cycloserine

Pregnancy Category-C

Schedule H

Indications *Tuberculosis resistant to first-line drugs.*

Availability **CAPSULE/TABLET** 250 mg.

Dose ***Oral***

Adult- Initially 250 mg every 12 h for 2 weeks, increase according to blood concentration and response to 500 mg every 2 h.

Child- Initially 10 mg/kg body weight daily adjusted to blood concentration and response.

Contraindications Severe renal impairment; epilepsy; depression, severe anxiety, psychotic states, alcohol dependence; porphyria; hypersensitivity.

Precautions Reduce dose in renal impairment (avoid if severe); monitor haematological, renal and hepatic function; lactation; discontinue or reduce dose if allergic skin reactions or CNS toxicity occur, pregnancy (Appendix 7c).

Adverse Effects Mainly neurological, including headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression (discontinue or reduce dose if symptoms of CNS toxicity); rashes, allergic dermatitis (discontinue or reduce dose); megaloblastic anaemia; changes in liver function tests; heart failure at high doses reported.

Storage Store at a temperature not exceeding 30°C (tablets). Store protected from moisture (capsules).

Ethambutol *

Pregnancy Category-C

Schedule H

Indications	*Tuberculosis, in combination with other drugs.*
Availability	**TABLETS** 200, 400, 600, 800 mg and 1g.
Dose	***Oral***
	Adult- 15 mg/kg body weight as a single dose, retreatment with 25 mg/kg body weight as a single dose for two months, thereafter reduce to 15 mg/kg body weight. Given as combination therapy with other anti-tubercular drugs.
	Child- Same as for Adult. Do not use under 3 years.
Contraindications	Optic neuritis; children under 5 years-unable to report symptomatic visual disturbances; severe renal impairment; hypersensitivity.
Precautions	Visual disturbances-ocular examination recommended before and during treatment (see note below); reduce dose in renal impairment (Appendix 7d) and monitor plasma concentration; elderly; pregnancy (Appendix 7c) (not known to be harmful); lactation.

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

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; pulmonary infiltrates gastrointestinal upset.
Storage	Store protected from moisture.

Isoniazid*

Pregnancy Category-C

Schedule H

Indications	*Tuberculosis, in combination with other drugs; tuberculosis prophylaxis also.*
Availability	**TABLETS** 100 and 300 mg.
Dose	***Oral***

Adult- 3 to 5 mg/kg body weight up to 300 mg as single dose daily.

Child- 10 to 15 mg/kg body weight as a single dose, not to exceed 300 mg/day.

Contraindications Drug-induced Hepatic Disease.

Precautions Hepatic impairment (monitor hepatic function; Appendix 7a); malnutrition, chronic alcohol dependence, chronic renal failure (Appendix 7d); 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 (Appendix 7c) (not known to be harmful); lactation (Appendix 7b); porphyria; interactions (Appendix 6a, 6c, 6d).

Patients or their caretakers 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.

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; memory impairement, elevated serum transaminase, rheumatic syndrome, pyridoxine syndrome.

Storage Store protected from light.

Kanamycin

Pregnancy Category-D

Schedule H

Indications *Tuberculosis; hepatic coma; penicillin resistant gonorrhoea, chronic bacterial infections.*

Availability **INJECTION Vial** 500, 750 mg and 1g.

Dose ***Intramuscular and intravenous injection***

Adult- 1g daily as a single dose.

Child- 6 to 15 mg/kg body weight daily in divided doses, 8 to 12 h (slow injection), usual duration of therapy 7 to 10 days.

Contraindications Lactation; pregnancy (Appendix 7c); hypersensitivity; renal impairment.

Precautions Myasthenia gravis; renal impairment; elderly patients with neuromuscular disorder.

Adverse Effects Nephrotoxicity; ototoxicity; skin rash; urticaria; neuromuscular blockade; malabsorption syndrome.

Storage Store protected from light and moisture.

Pyrazinamide*

Pregnancy Category-C

Schedule H

Indications *Tuberculosis, in combination with other drugs.*

Availability **TABLETS** 300, 500 and 750 mg; 1 and 1.5g; **SUSPENSION** 100 ml (5%).

Dose ***Oral***

Adult and Child- 20 to 35 mg/kg body weight as a single dose (max. 3g daily).

Contraindications Severe hepatic impairment; porphyria.

Precautions Hepatic impairment (monitor hepatic function; (Appendix 7a); renal impairment (Appendix 7d); diabetes mellitus (monitor blood glucose-may change suddenly); gout; pregnancy (Appendix 7c) and lactation; hypouricemia.

Patients or their caretakers 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.

Adverse Effects Hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting; arthralgia; gout; sideroblastic anaemia; rash, photosensitivity; porphyria, dysuria, thrombocytopenia, hyperplasia, myalgia.

Storage Store in single dose containers protected from light and moisture.

Rifampicin* (Refer Page No. 190)

Pregnancy Category-C

Schedule H

Indications *Tuberculosis, in combination with other drugs.*

Availability **CAPSULE** 150, 300, 350, 450, 500, 600 and 750 mg; **SUSPENSION** 100 mg/5 ml.

Dose ***Oral***

Adult- 450 to 600 mg as a single dose before breakfast.

Child- 10 to 20 mg/kg body weight daily, same dose for meningococcal carriers but for 4 days.

Contraindications Hypersensitivity; jaundice.

Precautions Reduce dose in hepatic impairment (Appendix 7a); 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); lactation; porphyria; discolours soft contact lenses; advise patients on oral contraceptives to use additional means; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c); cerebral haemorrhage, visual disturbances.

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

Patients or their caretakers 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.

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 max. dose of 600 mg daily); oedema, 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.

Storage Store protected from light and moisture.

Rifampicin + Isoniazid

Pregnancy Category-C

Schedule H

Indications *Tuberculosis.*

Availability

TABLETS/CAPSULES

Rifampicin	+	Isoniazid
60 mg	+	30 mg
100 mg	+	100 mg
100 mg	+	300 mg
100 mg	+	50 mg
150 mg	+	100 mg
150 mg	+	75 mg
300 mg	+	150 mg
450 mg	+	300 mg
600 mg	+	300 mg

Dose

Adult- One tablet daily before breakfast.

Precautions

Combined preparation usually not suitable for use in children; see under Rifampicin and Isoniazid; pregnancy (Appendix 7c).

Storage

Store protected from moisture.

Rifampicin + Isoniazid + Ethambutol

Pregnancy Category-C

Schedule H

Indications

Tuberculosis.

Availability

TABLETS

Rifampicin	+	Isoniazid	+	Ethambutol
150 mg	+	275 mg	+	275 mg
150 mg	+	75 mg	+	275 mg
450 mg	+	300 mg	+	800 mg
450 mg	+	225 mg	+	825 mg
100 mg	+	50 mg	+	800 mg
300 mg	+	150 mg	+	550 mg

CAPSULES

Rifampicin	+	Isoniazid	+	Ethambutol
225 mg	+	150 mg	+	400 mg

Dose

One tablet daily before breakfast in accordance with dose of individual drugs.

Precautions

Pregnancy (Appendix 7c).

Storage

Store protected from moisture.

Rifampicin + Isoniazid + Pyrazinamide

Pregnancy Category-C

Schedule H

Indications

Tuberculosis, in combination with other drugs.

Availability

TABLETS/CAPSULES

Rifampicin	+	Isoniazid	+	Pyrazinamide
60 mg	+	30 mg	+	150 mg
100 mg	+	50 mg	+	300 mg
150 mg	+	100 mg	+	500 mg
450 mg	+	300 mg	+	1000 mg
120 mg	+	80 mg	+	250 mg
225 mg	+	150 mg	+	750 mg
150 mg	+	100 mg	+	375 mg
450 mg	+	300 mg	+	1500 mg

Dose

Oral

Adult- One tablet daily before breakfast.

Contraindications

Combined preparation not suitable for use in children; see Rifampicin, Isoniazid and Pyrazinamide; pregnancy (Appendix 7c).

Storage

Store protected from moisture.

Rifampicin + Isoniazid + Pyrazinamide + Ethambutol

Pregnancy Category-C

Schedule H

Indications

Tuberculosis.

Availability

TABLETS

Rifampicin	+	Isoniazid	+	Pyrazinamide	+	Ethambutol
150 mg	+	100 mg	+	500 mg	+	800 mg
225 mg	+	150 mg	+	750 mg	+	400 mg
150 mg	+	75 mg	+	400 mg	+	275 mg
150 mg	+	100 mg	+	500 mg	+	267 mg
450 mg	+	300 mg	+	1500 mg	+	800 mg
600 mg	+	300 mg	+	800 mg	+	1100 mg
1450 mg	+	225 mg	+	1200 mg	+	825 mg

Dose

Oral

Adult- One tablet daily before breakfast.

Precautions

Pregnancy (Appendix 7c).

Storage

Store protected from moisture.

Streptomycin*

Pregnancy Category-D

Schedule H

Indications

Tuberculosis, in combination with other drugs.

Availability

INJECTION vial 750 mg and 1g.

Dose

Deep intramuscular injection.

Adult- 0.75g to 1g daily.

Elderly- 0.5g daily.

Child- 20 to 40 mg/kg body weight daily.

Contraindications Hearing disorders; myasthenia gravis; pregnancy (Appendix 7c).

Precautions **Children-**painful injection, avoid use if possible; renal impairment (Appendix 7d), infants and elderly (dosage adjustment and monitor renal, auditory and vestibular function and plasma streptomycin concentrations); interactions (Appendix 6c).

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.

Storage Store protected from moisture.

Thiacetazone + Isoniazid

Pregnancy Category-C

Schedule H

Indications *Tuberculosis, in combination with other drugs.*

Availability **TABLETS**

Thiacetazone	+	Isoniazid
150 mg	+	300 mg
37.5 mg	+	750 mg

Dose ***Oral***

Adult- One tablet daily before breakfast.

Contraindications See Isoniazid; hepatic impairment; renal impairment; HIV infection-thioacetazone associated with high incidence of serious, sometimes fatal cutaneous hypersensitivity reactions, including exfoliative dermatitis.

Precautions See Isoniazid; determine efficacy and toxicity of thiacetazone-geographical differences; hypersensitivity reactions-withdraw treatment; Pregnancy (Appendix 7c).

Adverse Effects See Isoniazid; thiacetazone causes the following-nausea, vomiting, diarrhoea; hypersensitivity reactions including conjunctivitis, vertigo, rashes; fatal exfoliative dermatitis, acute hepatic failure reported; also, agranulocytosis, thrombocytopenia and aplastic anaemia.

Storage Store protected from light and moisture.

DOTS (Directly Observed Treatment, Short Course)

The WHO-recommended Directly Observed Treatment, Short Course (DOTS) strategy was launched formally as Revised National TB Control Programme in India in 1997 after pilot testing from 1993-1996. Since then DOTS has been widely advocated and successfully applied. (Revised National TB Control Policy)

DOTS is the most effective strategy available for controlling TB.

The five key components of DOTS are

a) Political commitment to control TB;
b) Case detection by sputum smear microscopy examination among symptomatic patients;
c) Patients are given anti- TB drugs under the direct observation of the health care provider/community DOT provider;
d) Regular, uninterrupted supply of anti-TB drugs; and
e) Systematic recording and reporting system that allows assessment of treatment results of each and every patient and of whole TB control programme.

Responsibility of ensuring regular and complete treatment of the patient lies with the health system.

In 2006, the new stop TB strategy was recommended internationally by WHO. The components of the new stop TB strategy are the following:

1. Pursue high quality DOTS expansion and enhancement
2. Address TB/HIV, MDR-TB and other challenges
3. Contribute to health system strengthening
4. Engage all health care providers
5. Empower people with TB and communities
6. Enable and promote research

DOTS involves treatment with combination of drugs -Rifampicin 300 mg + Isoniazid 150 mg + Pyrazinamide 800 mg + Ethambutol 550 mg, given thrice weekly. Twice weekly therapy can also be given but it is not recommended since it does not have margin for error and missing even one dose makes the therapy ineffective.

9.9 Antipneumocystosis and Antitoxoplasmosis Drugs

Pneumocystosis:

Pneumocystis carinii is classified as a protozoan although there is evidence to suggest that it is probably a fungus. *Pneumocystis carinii* pneumonia is probably acquired by the airborne route. In otherwise healthy persons it rarely, produces signs of infection. However, it is a frequent cause of opportunistic infection in immunosuppressed, debilitated or malnourished patients; it is the commonest cause of pneumonia in AIDS and the most frequent immediate cause of death in these patients.

Sulfamethoxazole with trimethoprim is the treatment of choice for *Pneumocystis carinii* pneumonia and is also used for prophylaxis in high-risk patients; pentamidine isothionate is used in patients unresponsive to or intolerant of sulfamethoxazole with trimethoprim.

The treatment of *Pneumocystis carinii* infections must only be undertaken with specialist supervision where there are appropriate monitoring facilities.

Toxoplasmosis:

Toxoplasmosis is caused by infection with the protozoan parasite *Toxoplasma gondii*. Most infections are self-limiting and do not require treatment. However, in immunodeficiency, primary infection may result in encephalitis, myocarditis or pneumonitis; impairment of immunity (such as in AIDS) in a previously infected person, may result in encephalitis or meningoencephalitis. Congenital transmission may occur if there is a primary infection in early pregnancy or if the mother is immunodeficient. Such cases often result in spontaneous abortion, fetal death or severe congenital disease. Ocular toxoplasmosis causes chorioretinitis and is often the result of a childhood infection that becomes apparent in adulthood.

The treatment of choice for toxoplasmosis is pyrimethamine with sulfadiazine; a folate supplement is also given to counteract the megaloblastic anaemia associated with these drugs.

Pentamidine* **(Refer Page No 175)**

9.10 Antiretrovirals

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 introduced. Other nucleoside reverse transcriptase inhibitors include abacavir, didanosine, lamivudine, stavudine and zalcitabine.

The protease inhibitors include amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir. 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, nelfinavir, ritonavir and possibly saquinavir 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

plus

a non-nucleoside reverse transcriptase inhibitor

or a third nucleoside reverse transcriptase inhibitor

or a protease inhibitor which may be combined with ritonavir as booster.

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, nevirapine, nelfinavir and saquinavir 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.

Lactation:

Antiretroviral drugs may be present in breastmilk and may reduce viral load in breastmilk and reduce the risk of transmission through lactation. 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 lactation and, where possible, they should limit or avoid lactation; in particular, lactation 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 health-care 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.

9.10.1 Nucleoside/Nucleotide 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

Pregnancy Category-C

Schedule H

Indications	*HIV infection in combination with atleast two other antiretroviral drugs.*
Availability	**TABLET** 300 mg.
Dose	***Oral***
	Adult- 300 mg twice daily or 600 mg once daily.

Child- 3 months to 12 years: 8 mg/kg body weight every 12 h (max. 600 mg daily).

Contraindications

Pregnancy (Appendix 7c); lactation (Appendix 7b); hepatic dysfunction (Appendix 7a); renal disease.

Precautions

Hepatic impairment (see below and Appendix 7a); renal impairment; pregnancy (see notes above and Appendix 7c); lactation (Appendix 7b) (see notes above); hypersensitivity reaction; interactions (Appendix 6a).

Adverse Effects

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 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 diagnosis 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.

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.

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.

Storage

Store at a temperature not exceeding 30°C.

Didanosine*

Pregnancy Category-B

Schedule H

Indications

HIV infection in combination with atleast two other antiretroviral drugs.

Availability

TABLETS 100, 250 mg and 400 mg; **CAPSULES** 250 and 400 mg.

Dose

Oral

Adult- Under 60 kg: 250 mg daily in 1 to 2 divided doses. 60 kg and over: 400 mg daily in 1 to 2 divided doses, 30 min before meals or 2 h after meals.

Child- 2week - 8 months: 100 mg/m^2 twice daily.
>8 months: 120 mg/m^2 twice daily.

Contraindications

Hypersensitivity; pancreatitis; co-administration of allopurinol and ribavirin.

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 7d and 7a); pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur; interactions (Appendix 6c, 6d); immune reconstitution syndrome, fat redistribution, retinal changes and optic neuritis.

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 isothionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated.

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

Adverse Effects Pancreatitis (see also under Precautions); peripheral neuropathy especially in advanced HIV infection-suspend (reduced dose may be tolerated when symptoms resolve); hyperuricaemia (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.

Storage Store protected from light.

Emtricitabine

Pregnancy Category-B

Schedule H

Indications *HIV infection.*

Availability **CAPSULE** 200 mg.

Dose ***Oral***

Adult and child over 33 kg- 200 mg once a day.

Child- Under 33 kg: 6 mg/kg body weight once a day.

Contraindications Lactation; hypersensitivity.

Precautions Monitor patients with hepatitis B (risk of exacerbation of hepatitis); obesity, lactic acidosis, severe hepatomegaly, co-infection with hepatitis B virus; pregnancy (Appendix 7c).

Adverse Effects Gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea); anorexia; pancreatitis; liver damage (see also Lactic Acidosis, above); dyspnoea; cough, headache; insomnia; dizziness; fatigue; blood disorders (including anaemia, neutropenia and thrombocytopenia); myalgia, arthralgia, rash, urticaria and fever. Lipodystrophy, abnormal dreams, pruritus and hyperpigmentation.

Storage Store protected from moisture.

Lamivudine*

Pregnancy Category-C

Schedule H

Indications *HIV infection in combination with at least two other antiretroviral drugs.*

Availability **TABLETS** 100, 150 and 300 mg; **ORAL SOLUTION** 50 mg/ml.

Dose

Oral

Adult- 150 mg twice daily administered with zidovudine.

Child- 3 months to 12 years: 4 mg/kg body weight twice a day (max. 150 mg twice daily).

Contraindications

Pregnancy (Appendix 7c); lactation (Appendix 7b); hepatic dysfunction (Appendix 7a); renal disease (Appendix 7d).

Precautions

Renal impairment (Appendix 7d); hepatic disease (see below); pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6c).

Potentially life-threatening lactic acidosis and severe hepatomegaly 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.

Adverse Effects

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.

Storage

Store protected from moisture.

Stavudine*

Pregnancy Category-C

Schedule H

Indications

HIV infection in combination with atleast two other antiretroviral drugs.

Availability

TABLETS/CAPSULES 30 and 40 mg.

Dose

Oral

Adult- Under 60 kg: 30 mg every 12 h preferably at least 1 h before food.
60 kg and over: 40 mg every 12 h.

Neonate under 2 weeks- 500 µg/kg body weight.

Child- over 2 weeks and body weight under 30 kg: 1 mg/kg body weight every 12 h.
30 kg and over: 30 mg every 12 h.

Contraindications Hypersensitivity.

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; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); fat redistribution, immune reconstitution syndrome.

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.

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.

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.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Tenofovir

Pregnancy Category-B

Schedule H

Indications *HIV infection.*

Availability **TABLET** 300 mg.

Dose ***Oral***

Adult- 300 mg once daily.

Contraindications Lactation; hypersensitivity.

Precautions Should be used with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects), in hepatic impairment, in renal impairment and in pregnancy (Appendix 7c). Test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases; concomitant or recent use of nephrotoxic drugs; on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis).

Adverse Effects Gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea); anorexia; pancreatitis; liver damage; dyspnoea; cough; headache, insomnia, dizziness, fatigue; blood disorders (including anaemia, neutropenia and thrombocytopenia); myalgia, arthralgia, rash, urticaria and fever. See notes above for metabolic effects and lipodystrophy; hypophosphataemia; reduced bone density; nephrogenic diabetes insipidus and renal failure; lactic acidosis, decrease in bone mineral density, acute exacerbation of hepatitis.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Zidovudine (AZT)*

Pregnancy Category-C

Schedule H

Indications *HIV infection in combination with at least two other antiretroviral drugs; monotherapy for prevention of maternal-fetal HIV transmission.*

Availability **TABLETS** 30, 40, 100 and 300 mg; **CAPSULES** 100 and 300 mg; **SYRUP** 50 mg/5 ml.

Dose ***Oral***

HIV infection

Adult- 600 mg daily in divided doses in combination with other antiretroviral drugs.

Child- 6 weeks to 12 years: 160 mg/m^2 every 8 hour, max. dose 200 mg every 8 hour.

Prevention of maternal-foetal HIV transmission.

Adult- 100 mg five times daily or 200 mg thrice daily or 300 mg twice daily, start treatment after 14th week of gestation until the start of labour.

Prevention of HIV transmission in neonates.

Child- neonates- 2 mg/kg every 6 hour for first 6 weeks of life, starting with12 hour after birth.

Contraindications Abnormally low neutrophil counts or haemoglobin; neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase; life threatening allergic reactions.

Precautions Haematological toxicity; vitamin B_{12} deficiency (increased risk of neutropenia); reduce dose or interrupt treatment if anaemia or myelosuppression; renal impairment (Appendix 7d); hepatic impairment (Appendix 7a); risk of lactic acidosis; elderly; lactation (Appendix 7b); interactions (Appendix 6c, 6d); pregnancy (Appendix 7c); myopathy, use with interferon and ribavirin based regimens in HIV/HCV coinfected patients, immune reconstitution syndrome.

Adverse Effects Anaemia (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; malaise; anorexia; asthenia; myopathy; myalgia; pancytopenia, thrombocytopenia; gynaecomastia; urinary frequency; rash, pruritus, pigmentation of nail, skin and oral mucosa.

Storage Store protected from light and moisture.

9.10.2 Non-Nucleoside Transcriptase Inhibitor

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*

Pregnancy Category-D

Schedule H

Indications *HIV infection in combination with at least two other antiretroviral drugs.*

Availability **TABLETS/CAPSULES** 200, 400 and 600 mg.

Dose ***Oral***

Adult- 600 mg once a day.

Child- Over 3 years
13 to 14 kg body weight: 200 mg once a day.
15 to 19 kg body weight: 250 mg once a day;
25 to 32.5 kg body weight: 400 mg once a day;
over 40 kg body weight: adult dose.

Contraindications Pregnancy (see notes above and (Appendix 7c); substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured); hypersensitivity.

Precautions Hepatic impairment (avoid if severe; Appendix 7a); severe renal impairment; lactation (Appendix 7b) (see notes above); elderly; history of mental illness or substance abuse; interactions (Appendix 6b, 6c); psychiatric symptoms.

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.

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.

Storage Store protected from light.

Nevirapine*

Pregnancy Category-C

Schedule H

Indications *HIV infection, in combination with at least two other antiretroviral drugs; prevention of mother-to-child transmission in HIV-infected patients.*

Availability **TABLET/CAPSULE** 200 mg;
ORAL SUSPENSION 100 mg/5 ml.

Dose ***Oral***

Adult- 200 mg once a day for 14 days, if tolerated and no rash is observed then increase to 200 mg two times a day.

Child- 2 months to 8 years: 4 mg/kg body weight once a day for 14 days, if tolerated and no rash is observed increase to 4 mg/kg body weight two times a day.

Contraindications

Acute porphyria; severe hepatic impairment; post-exposure prophylaxis; breast feeding.

Precautions

Hepatic impairment (see below and Appendix 7a); history of chronic hepatitis (greater risk of hepatic adverse effects), pregnancy (Appendix 7c) and lactation (Appendix 7b); interactions (Appendix 6b, 6c).

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, 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.

Patients should be told how to recognize hypersensitivity reactions and advised to seek immediate medical attention if symptoms develop.

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; granulocytopenia.

Storage

Store protected from light and moisture at a temperature not exceeding 30°C.

9.10.3 Combinations

Lamivudine + Nevirapine + Stavudine*

Pregnancy Category-C

Schedule H

Indications *HIV infection.*

Availability **TABLETS**

Lamivudine	+	Nevirapine	+	Stavudine
40 mg	+	10 mg	+	70 mg
150 mg	+	40 mg	+	200 mg
150 mg	+	30 mg	+	200 mg
100 mg	+	30 mg	+	200 mg

Dose **Adult-** One tablet twice daily. Patients with body weight less than 50 kg, 2 mg/kg body weight two times a day.

Child- 3 months to 12 years; half adult dose is given two times a day.

Precautions Pregnancy (Appendix 7c).

Storage Store protected from moisture at a temperature not exceeding 25°C for DT.

Lamivudine + Zidovudine*

Pregnancy Category-C

Schedule H

Indications *HIV infection.*

Availability **TABLET** lamivudine + zidovudine 150 mg + 300 mg.

Dose **Adult-** 2 tablets three times a day or as prescribed.

Child- Half the adult dose.

Precautions Pregnancy (Appendix 7c).

Storage Store protected from moisture.

Zidovudine + Lamivudine + Nevirapine*

Schedule H

Indications *HIV infection.*

Avaialbility: **TABLETS** Zidovudine 300 mg + Lamivudine 150 mg + Nevirapine 200 mg.

Dose **Adult-** 2 tablets three times a day.

Child- Half adult dose.

9.10.4 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*

Pregnancy Category-C

Schedule H

Indications	*HIV infection in combination with two nucleoside reverse transcriptase inhibitors and usually with low-dose ritonavir booster.*
Availability	**TABLET/CAPSULE** 400 mg.
Dose	***Oral*** **Adult-** 800 mg every 8 h with water, 1 h before or 2 h after meals. **Child-** 4 to 17 years: 500 mg every 8 h. Safety and efficacy is not established in patients less than 4 years.
Contraindications	Pregnancy; concurrent use of cisapride; alprazolam; midazolam.
Precautions	Hepatic impairment (Appendix 7a); ensure adequate hydration to reduce risk of nephrolithiasis; diabetes mellitus; haemophilia; pregnancy (see notes above and Appendix 7c); lactation (Appendix 7b) (see notes above); metabolism of many drugs inhibited if administered concomitantly; interactions (Appendix 6c, 6d); hyperbilirubinemia, tubulo-interstitial nephritis.
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; hydronephrosis.
Storage	Store protected from light and moisture at a temperature not exceeding 30°C.

Lopinavir + Ritonavir

Pregnancy Category-C

Schedule H

Indications — *HIV infection in combination with two other antiretroviral drugs.*

Availability — **CAPSULE/TABLET** Lopinavir + Ritonavir 200 mg + 50 mg.

Dose — **Adult and child with body surface area 1.4 m^2, body weight 40 kg and over**- 2 tablets twice daily.

Child over 2 years with body weight 40 kg and body surface area 0.5 to 0.9 m^2 - 2 tablets (Lopinavir 100 mg + Ritonavir 25 mg), twice daily. Body surface area 0.9 to 1.4 m^2 - 3 tablets twice daily.

Note: Ritonavir increases effect of lopinavir; low dose in combination does not have intrinsic antiviral activity.

Contraindications — Hypersensitivity; avoid concomitant use with ergot derivatives.

Precautions — Hepatic impairment-avoid if severe; renal impairment; haemophilia; pregnancy (see notes above and (Appendix 7c); lactation (see notes above and Appendix 7b); diabetes mellitus.

Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated-discontinue if pancreatitis diagnosed.

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 discolouration, 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; myocardial infarction, loss of taste.

Storage Store protected from moisture at a temperature not exceeding 30°C for tablets and store protected from moisture in refrigerator (2 to 8°C) for capsules.

Nelfinavir*

Pregnancy Category-B

Schedule H

Indications *HIV infection in combination with two other antiretroviral drugs.*

Availability **TABLET** 250 mg.

Dose **Adult-** 750 mg thrice daily.

Child- 3 to 13 years: initially 25 to 30 mg/kg body weight three times a day (max. 1.25 g) or 50 to 55 mg/kg body weight twice daily. Not recommended under 3 years.

Contraindications Moderate to severe liver disease; concurrent use of alprazolam; midazolam; lactation; hypersensitivity.

Precautions Hepatic and renal impairment; diabetes mellitus; haemophilia; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6b, 6c, 6d); HIV cross resistance, immune reconstitution syndrome.

Adverse Effects Diarrhoea, nausea, vomiting, flatulence, abdominal pain; rash; reports of elevated creatine kinase; hepatitis; pancreatitis; neutropenia; hypersensitivity reactions including bronchospasm, fever, pruritus and facial oedema, lipodystrophy and metabolic effects, see notes above; backpain, myopathy, anxiety, sleep disorder, kidney calculus, QT prolongation.

Storage Store protected from light.

Oseltamivir

Pregnancy Category-C

Schedule X

Indications *Influenze A, B and its subtypes like swine flu.*

Availability **CAPSULES** 30, 45 and 75 mg.

Dose ***Oral***

Adult and adolescent- Prevention of influenza, over 13 years: 75 mg once daily for 10 days for post exposure prophylaxis, for up to 6 weeks in epidemics. Treatment of influenza, over 13 years: 75 mg every 12 h for 5 days.

Child- Prevention of influenza: body weight under 15 kg: 30 mg once daily; 15 to 23 kg: 45 mg once daily; 23 to 40 kg: 60 mg once daily: above 40 kg: adult dose.

Treatment of influenza: body weight under 15 kg: 39 mg every 12 h for 5 days; 15 to 23 kg: 45 mg every 12 h for 5 days; 23 to 40 kg: 60 mg every 12 h for 5 days; above 40 kg: adult dose.

Contraindications Hypersensitivity.

Precautions Hepatic impairment; pregnancy (Appendix 7c); lactation; renal impairment.

Adverse Effects Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness; conjunctivitis, epistaxis; rash; very rarely, hepatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis; neuropsychiatric disorders also reported (in children); cough, bronchitis, eczema, seizures, aggravation of diabetes.

Storage Store protected from moisture and light at a temperature not exceeding 30°C.

Ritonavir*

Pregnancy Category-C

Schedule H

Indications *HIV infection, as a booster to increase effect of indinavir, lopinavir or saquinavir and in combination with two other antiretroviral drugs.*

Availability **TABLET** 100 and 250 mg; **CAPSULE** 100 mg; **SYRUP** 400 mg/5 ml.

Dose **Adult-** Initially 300 mg every 12 h for three days increased in steps of 100 mg every 12 h over not longer than 14 days to 600 mg every 12 h.

Child- Over 2 years: initially 250 mg/m^2 of body surface area every 12 h, increase by 50 mg/m^2 at intervals of 2 to 3 days to 350 mg/m^2 body surface area every 12 h (max. 600 mg/12 h).

Contraindications Severe hepatic impairment.

Precautions Hepatic impairment, diabetes mellitus; haemophilia; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6b, 6c, 6d); PR interval prolongation, lipid disorder.

Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated-discontinue if pancreatitis diagnosed.

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; postural hypotension, abnormal stool, albuminuria.

Storage Store protected from light at temperature (2 to 8°C) for capsules.

Saquinavir*

Pregnancy Category-B

Schedule H

Indications *HIV infection in combination with two other antiretroviral drugs and usually with low-dose ritonavir booster.*

Availability **TABLETS** 500 mg; **CAPSULES** 200 mg.

Dose **Adult and adolescent over 16 years** with low dose ritonavir, 1g saquinavir every 12 h.

Contraindications Hypersensitivity.

Precautions Hepatic impairment (Appendix 7a); renal impairment; diabetes mellitus; haemophilia; pregnancy (Appendix 7c) and lactation (Appendix 7b) (see notes above); interactions (Appendix 6d); hyperlipidemia, lactose intolerance, fat redistribution, immune reconstitution syndrome.

Adverse Effects Diarrhoea, buccal and mucosal ulceration, abdominal discomfort, nausea, vomiting; headache, peripheral neuropathy, paraesthesia, dizziness, insomnia, mood changes, ataxia, musculoskeletal pain, asthenia; fever, pruritus, rash and other skin eruptions, rarely, Stevens-Johnson syndrome; other rare adverse effects include thrombocytopenia and other blood disorders; liver damage; pancreatitis and nephrolithiasis; reports of elevated creatine kinase, raised liver enzymes and neutropenia when used in combination therapy; lipodystrophy and metabolic effects (see notes above); cyanosis, heart murmur; decrease appetite; amnesia.

Storage Store protected from moisture.

Zanamivir

Pregnancy Category-B

Schedule X

Indications *Most effective for the treatment of influenza if started within a few hour of the onset of symptoms; they are to be used within 48 h (36 h for children) of the first symptoms.*

Availability **CAPSULE** 5 mg, powder for inhalation.

Dose ***Oral-*** powder for inhalation.
Adult- minimum 10 mg (2 inhalations) inhaled; orally twice a day for 5 days. Max. 20 mg.

Note: The formulation is not designed or intended to be administred by nebulization. To be used with a diskhaler device only.

Precautions Anaphylaxis; encephalitis; pediatric, geriatric, lactation, pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness; conjunctivitis, epistaxis; rash; very rarely, hepatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

9.11 Antischistosomals and Antitrematode Drugs

Schistosomiasis:

Schistosomiasis, a waterborne parasitic infection, is caused by several species of trematode worms (blood flukes). Its socio-economic impact as a parasitic disease is outstripped only by that of malaria. Intestinal schistosomiasis is caused principally by *Schistosoma mansoni* as well as *S. japonicum, S. mekongi* and *S. intercalatum*. Urinary schistosomiasis is caused by *S. haematobium*. The latter is an important predisposing cause of squamous cell cancer of the bladder.

Praziquantel has transformed the treatment of schistosomiasis and is often effective in a single dose, against all species of the parasite. It can be of particular value in patients with mixed infections and those who do not respond adequately to other drugs. It is also extremely well tolerated and well suited for mass treatment control programmes. Extensive use over several years has provided no evidence of serious adverse effects or long-term toxicity, nor has mutagenic or carcino-genic activity been shown in experimental animals.

Drugs still widely used in the treatment of schistosomiasis include oxamniquine, which is effective against *S. mansoni*. It is preferable to delay treatment with oxamniquine in pregnant women until after delivery unless immediate intervention is essential. Due to lack of information on whether oxamniquine is excreted in breast milk, it is preferable not to administer it to nursing mothers.

Praziquantel*

Pregnancy Category-B

Schedule H

Indications	*Taenia saginata, T. solium, Hymenolepis nana and Diphyllobothrium latum infections; trematode infections, schistosomiasis.*
Availability	**TABLETS** 600 mg.
Dose	**Schistosomiasis**: 40 mg/kg body weight is given in two divided doses 4 to 6 h apart in one day. **S. japonicum infection**: 60 mg/kg body weight in three divided doses in one day.
Contraindications	Ocular cysticercosis; hypersensitivity.

Precautions

Pregnancy (Appendix 7c); lactation (Appendix 7b); areas endemic for cysticercosis-possible oedematous reaction; impaired renal function, cardiac irregularities.

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

Adverse Effects

Abdominal discomfort, anorexia, nausea, vomiting, malaise, headache, dizziness, drowsiness, rectal bleeding; rarely, hypersensitivity reactions, including fever, pruritus, eosinophilia (may be due to dead and dying parasites); ectopic rhythms, urticaria, erythema, convulsions.

Storage

Store protected from light.

9.12 Antiviral Drugs

Herpes and Cytomegalovirus Infections:

Herpes Simplex Virus (HSV):

Acyclovir 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 patients. Genital lesions, oesophagitis and proctitis may be treated with oral Acyclovir. HSV encephalitis or pneumonitis should be treated with intravenous Acyclovir.

Valacyclovir, a prodrug of Acyclovir, can be given by mouth as an alternative treatment for herpes simplex infections of the skin and mucous membranes (including initial and recurrent genital herpes).

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. Acyclovir 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.

Cytomegalovirus (CMV):

Parenteral antiviral ganciclovir arrests retinochoroiditis and enteritis caused by CMV in HIV infected patients. Maintenance therapy with oral ganciclovir should be given to prevent relapse of retinitis. Alternative therapy with intravenous foscarnet can be used if necessary.

Acyclovir* (Refer Page No. 550)

Pregnancy Category-B

Schedule H

Indications	*Treatment of primary genital herpes; disseminated Varicella-zoster in immunocompromised patients; Herpes simplex encephalitis; chicken pox.*
Availability	**TABLETS Plain/DT** 200, 400 and 800 mg; **SUSPENSION** 400 mg/5 ml; **INFUSION** 100 ml (after reconstitution) (250 mg); **OINTMENT** 5g (3%w/w); **DROPS** 5 ml (3% w/w); **CREAM** 5g (5% w/w).
Dose	***Oral***

Adult- Non-genital herpes simplex treatment, 200 mg five times daily usually for 5 days, longer if new lesions appear during treatment or if healing is incomplete. 400 mg for immunocompromised patients or if absorption is impaired.

Genital herpes simplex treatment; 200 mg 5 times daily for 5 days or 400 mg three times daily for three days. Longer if new lesions appear or healing is incomplete.

Immunocompromised or HIV positive patients; 400 mg is given five times daily for 7 to 10 days during first episode or 400 mg three times a day for 5 to 10 days during recurrent injection.

Herpes simplex prevention of recurrence; 200 mg 4 times daily or 400 mg twice daily reduced to 200 mg two or three times daily interrupted every 6 to 12 months.

Varicella and herpes zoster; 800 mg five times daily for 7 days.

Chicken pox; 800 mg five times daily for 7 to 10 days.

Intravenous infusion

Severe initial genital herpes, Varicella zoster, Herpes simplex infection; 5 mg/kg body weight every 8 h for five days.

Child- Under 2 years; half dose. Above 2 years; adult dose.

Varicella and herpes zoster; 20 mg/kg body weight (max. 800 mg) four times daily for 5 days, under 2 years 200 mg four times daily, for 2 to 5 years; 400 mg four times daily. Over 6 years; 800 mg four times daily.

Chicken pox; 20 mg/kg body weight (max 800 mg) four times daily for 5 days.

Contraindications Hypersensitivity; glaucoma; psychiatric disease; depression.

Precautions Maintain adequate hydration; renal impairment (Appendix 7d); lactation (Appendix 7b); pregnancy (Appendix 7c); paediatrics.

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; decrease in haematological indices; on intravenous infusion, severe local inflammation (sometimes resulting in ulceration), fever, agitation, tremor, psychosis and convulsions somnolence, visual abnormalities.

Storage

Store tablets protected from light. For infusion: Store protected from moisture in a sterile tamper evident container sealed so as to exclude micro-organisms at a temperature not exceeding 30^{o}C.

13. Cardiovascular Drugs

13.1 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 h.

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's 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 β2 (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's angina and in patients in whom alterations in cardiac tone may influence the angina threshold.

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 contrain-

dicated, verapamil is an alternative, provided left ventricular function is adequate.

Prinzmetal's Angina:

Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

Acetylsalicylic Acid* (Refer Page No. 4, 239 and 317)

Pregnancy Category-D

Indications — *As an antiplatelet agent for prophylaxis of myocardial infarction, stable angina; stable angina pectoris; stroke prohphylaxis.*

Atenolol*

Pregnancy Category-D

Schedule H

Indications — *Angina and myocardial infarction; arrhythmias; hypertension; migraine prophylaxis.*

Availability — **TABLETS** 12.5, 25, 50, and 100 mg; **INJECTION** ampoule 5 mg/ml (10 ml).

Dose

Oral

Adult- 50 mg once daily, increased if necessary to 50 mg twice daily or 100 mg once daily. Angina: 50 mg daily administered alone or with a diuretic, dose can be increased to 100 mg (over 100 mg has no added advantage). May also be administered in combination with a mlodipine besylate 2.5 or 5 mg.

Child- 1 to 1.3 mg/kg body weight once daily or divided every 12 h.

Intravenous injection

2.5 mg at a rate of 1 mg/min, repeat at 5 min interval to a max. 10 mg.

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; pheochromocytoma (unless used with alpha-blocker).

Precautions Avoid abrupt withdrawal especially in angina; may precipitate or worsen heart failure; acute myocardial infarction, pregnancy (Appendix 7c), thyrotoxicosis, pheochromocytoma; lactation (Appendix 7b); first-degree atrioventricular block; liver function deteriorates in portal hypertension; reduce dose in renal impairment; 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 6a, 6b, 6c).

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).

Diltiazem

Pregnancy Category-C

Schedule H

Indications *Angina pectoris due to coronary artery spasm; chronic stable angina; cardiac arrhythmia.*

Availability **TABLETS/TABLETS (SR)** 30, 60, 90, 120, 180 and 240 mg; **CAPSULE** 60, 90, 120, 180 and 240 mg; **INJECTION** 5 ml (25 mg/5 ml).

Dose ***Oral***

Adult-30 mg 2 to 5 times a day before food and at night (bed time), increase gradually to 240 mg in 3 to 4 divided doses daily.

Child- Not recommended.

Cardiac arrhythmia

Adult-Initially 250 µg/kg by i.v. bolus over 2 min.

Contraindications Severe bradycardia; left ventricular failure with pulmonary congestion; second- or third-degree AV block (unless pacemaker fitted); sick sinus syndrome; lactation.

Precautions Reduce dose in hepatic and renal impairment; heart failure or significantly impaired left ventricular function; bradycardia (avoid if severe); first degree AV block; or prolonged PR interval; interactions (Appendix 6c); sinoatrial nodal dysfunction; pregnancy (Appendix 7c).

Adverse Effects Bradycardia, sino-atrial block, AV block; palpitation; dizziness; hypotension, malaise; asthenia; headache; hot flushes; gastro-intestinal disturbances; oedema (notably of ankles); rarely, rashes (including erythema multiforme and exfoliative dermatitis), photosensitivity; hepatitis; gynaecomastia; gum hyperplasia; extrapyramidal symptoms; depression reported; gastrointestinal haemorrhage; sinus arrest.

Storage Store protected from light.

Esmolol* (Refer Page No. 296)

Glyceryl Trinitrate*

Pregnancy Category-C

Schedule H

Indications *Prophylaxis and treatment of angina, myocardial infarction; post operative hypertension; cardio-pulmonary edema.*

Availability **TABLETS** 0.5, 2.6 and 6.4 mg; **CAPSULES** 2.5 and 6.4 mg; **INJECTION** 5 and 10 ml (5 mg/ml); **SUBLINGUAL TAB** 500 µg. **SPRAY** 0.4 mg/puff (200 mdi)

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.

Dose ***Sublingual***

Adult- 0.5 to 1 mg, repeated as required.

Intravenous infusion

10 to 200 µg/min.

Contraindications Hypersensitivity to nitrates; hypotension; hypovolaemia; raised intracranial pressure; 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; gastrointestinal hypermotility; malabsorption syndrome; hypothermia; recent history of myocardial infarction; interactions (Appendix 6b, 6c).

Adverse Effects Throbbing headache; flushing; dizziness, postural hypotension; tachycardia (paradoxical bradycardia also reported); abdominal pain; collapse; neurological deficit.

Storage Store protected from light and moisture in glass container of not more than 100 tablets at a temperature not exceeding 30°C. The container should be closed by means of screw cap lined with aluminium or tin foil. Cotton, wool wadding or other additional packing that absorbs glyceryl trinitrate should be avoided.

Isosorbide-5-Mononitrate*

Pregnancy Category-C

Schedule H

Indications *Prophylaxis and treatment of angina, congestive heart failure.*

Availability **TABLETS** 10, 20, 40, 50 and 60 mg; **TABLETS** (SR) 50 mg and 60 mg; **CAPSULE** 30, 40 and 60 mg.

Dose ***Oral***

20 mg 2 to 3 times a day initially, or 40 mg twice daily (max 120 mg daily individual dose).

Contraindications Hypersensitivity to nitrates; hypotensive conditions and hypovolaemia; hypertrophic cardiomyopathy; aortic stenosis; cardiac tamponade; constrictive pericarditis; mitral stenosis; marked anaemia; glaucoma; obstructive cardiomyopathy; raised intracranial pressure.

Precautions Hypothyroidism; malnutrition; hypothermia; head trauma; cerebral haemorrhage; gastrointestinal disease; recent history of myocardial infarction; hypoxaemia or other ventilation and perfusion abnormalities; susceptibility to angle-closure glaucoma; metal-containing transdermal systems should be removed before cardioversion or diathermy; avoid abrupt withdrawal; tolerance; severe hepatic impairment; severe renal impairment; pregnancy (Appendix 7c); lactation; interactions (Appendix 6a).

Adverse Effects

Postural hypotension, tachycardia (but paradoxical bradycardia also reported); throbbing headache; dizziness; less commonly nausea; vomiting; heartburn; flushing; temporary hypoxaemia; rash; application site reactions with transdermal patches; very rarely, angle-closure glaucoma; decreased cardiac output; urinary and faecal incontinence.

Specific side-effects following injection (particularly if given too rapidly) include severe hypotension, diaphoresis, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, abdominal pain, syncope; prolonged administration has been associated with methaemoglobinaemia.

Storage

Store at a temperature not exceeding 30°C.

Isosorbide Dinitrate*

Pregnancy Category-C

Schedule H

Indications

Prophylaxis and treatment of angina; heart failure.

Availability

TABLETS (sublingual) 5 and 10 mg; **CAPSULES** (timed release) 20 and 40 mg.

Dose

Sublingual

Adult- Angina acute attack: 5 to 10 mg, repeated as required.

Angina prophylaxis: 120 mg daily in divided doses.

Angina prophylaxis: 20 to 120 mg.

Contraindications

Hypersensitivity to nitrates; hypotension; hypovolaemia; myocardial infarction; 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 6a, 6b, 6c, 6d); pregnancy (Appendix 7c).

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-h rather than a 12-h interval, thus ensuring a nitrate-free interval each day.

Adverse Effects Throbbing headache; flushing; dizziness, postural hypotension, tachycardia (paradoxical bradycardia also reported); palpitation, decreased cardiac output; confusion; increased intracranial pressure.

Storage Store at a temperature not exceeding 30°C.

Metoprolol*

Pregnancy Category-C

Schedule H

Indications *Supraventricular arrhythmia, angina pectoris, hypertension, myocardial infarction; migraine prophylaxis; hyperthyroidism, heart failure.*

Availability **TABLETS** 10, 25, 50 and 100 mg; **CAPSULE** 12.5, 25, 50 and 100 mg; **INJECTION** 100 mg/2 ml, 250 mg/2 ml, 500 mg/2 ml.

Dose

Oral

Heart failure: Initiating dose 12.5 - 25 mg once a day, Maximum dose: 200 mg once a day; Hypertension: initially 100 mg daily, increase if required to 200 mg in two divided doses (max 400 mg daily). Angina: 50 mg daily, up to 300 mg daily in 2 to 3 divided doses if necessary.

Intravenous injection

Arrhythmia: up to 5 mg at a rate of 1 to 2 mg per min, repeated after 5 min if necessary (max dose 10 to 15 mg). Arrythmia developing during anaesthesia: 2 to 4 mg during induction.

Contraindications Asthma (important: see Bronchospasm below), uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; pheochromocytoma (apart from specific use with alpha-blockers).

Beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

Precautions Avoid abrupt withdrawal especially in ischaemic heart disease, first-degree AV block, portal hypertension (risk of deterioration in liver function); diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked; history of hypersensitivity-may increase sensitivity to allergens and result in more serious hypersensitivity response; also may reduce response to adrenaline (epinephrine); reduce dose of oral propranolol in hepatic impairment; renal impairment; lactation; pregnancy (Appendix 7c).

Adverse Effects Gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders; peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm; dyspnoea; headache; fatigue; sleep disturbances; paraesthesia; dizziness; vertigo; psychosis; sexual dysfunction; purpura; thrombocytopenia; visual disturbances; exacerbation of psoriasis; alopecia; rarely, rashes and dry eyes (reversible on withdrawal); on infusion venous irritation and thrombophlebitis; agranulocytosis; hyperglycemia; myocardial depression.

Storage Store protected from light.

Propranolol* (Refer Page No. 236)

Pregnancy Category-C

Schedule H

Indications *Cardiac arrhythmias; tachycardia; hypertrophic obstructive cardiac myopathy; pheochromocytoma; thrombosis; management of angina; essential and renal hypertension; prophylaxis of migraine.*

Availability **TABLETS** 10, 20, 40, 60 and 80 mg plain; 40, 60 and 80 mg (SR); **CAPSULE** 40, 60 and 80 mg (SR); **INJECTION** 1 ml ampoule (1 mg/ml).

Dose ***Oral***

Adult- Hypertension: initially 40 mg twice a day or 80 mg once a day; increased at weekly intervals as required, maintenance 160 to 320 mg in three divided doses. Prophylaxis of variceal bleeding in portal hypertension: 40 mg twice daily, increased to 80 mg twice daily according to heart rate (max. 160g twice daily).

Angina: Initially 40 mg 3 times a day, maintenance 120 to 240 mg daily. Prophylaxis after myocardial infarction: 40 mg 4 times daily for 2 to 3 days, then 80 mg twice daily beginning 5 to 21 days after infarction.

Contraindications

Asthma (important: see Bronchospasm below); uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension; sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease, pheochromocytoma (apart from specific use with alpha-blockers); haemorrhage.

Beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

Precautions

Avoid abrupt withdrawal especially in ischaemic heart disease, first-degree AV block, portal hypertension (risk of deterioration in liver function), diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked; history of hypersensitivity- may increase sensitivity to allergens and result in more serious hypersensitivity response; also may reduce response to adrenaline (epinephrine); reduce dose of oral propranolol in hepatic impairment; renal impairment; lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6d); pregnancy (Appendix 7c).

Adverse Effects

Gastro-intestinal disturbances; bradycardia; heart failure, hypotension, conduction disorders; peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm; dyspnoea; headache; fatigue; sleep disturbances; paraesthesia; dizziness; vertigo; psychosis; sexual dysfunction; purpura; thrombocytopenia; visual disturbances; exacerbation of psoriasis; alopecia; rarely, rashes and dry eyes (reversible on withdrawal); on infusion venous irritation and thrombophlebtis; eosinophilia; hyperglycemia; cardiogenic shock; visual hallucinations.

Storage

Store protected from light and moisture. Injection: Store protected from light and moisture in a single dose container.

Verapamil*

Pregnancy Category-C

Schedule H

Indications — *Angina, including stable, unstable and Prinzmetal angina; arrhythmias; ischaemic heart disease; migraine.*

Availability — **TABLETS** 40, 80, 120 and 240 mg (SR); **INJECTION** 2 ml (5 mg/2 ml).

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

Dose

Oral

Adult- 80 to 120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina).

Supraventricular arrhythmias: 40 to 120 mg 3 times daily.

Intravenous injection

Adult- Supraventricular arrhythmias: 5 to 10 mg over 2 min (preferably with ECG monitoring).

Elderly- Paroxysmal tachyarrhythmias: 5 to 10 mg over 3 min, further 5 mg may be given after 5 to 10 min if required.

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; platelet dysfunction.

Precautions — First-degree atrioventricular block; kidney impairment; cirrhosis patients; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); hepatic impairment (Appendix 7a); children (specialist advice only); lactation; pregnancy (Appendix 7c); interactions (Appendix 6b, 6c).

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, 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), impotence; hepatotoxicity; hyperprolactinemia; myoclonic dystonia.

13.2 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 h 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 never be administered concomitantly because of the risk of hypotension and asystole.

Ventricular Tachycardia:

Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. In more stable patients intravenous lidocaine or 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.

Torsades de pointes is a special form of ventricular tachycardia associated with prolongation of the QT interval. Initial treatment with intravenous infusion of magnesium sulphate (usual dose 2g over 10-15 min, 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. Isoprenaline is an inotropic sympathomimetic; it increases the heart rate and therefore shortens the QT interval, but given alone it may induce arrhythmias.

Bradyarrhythmias:

Sinus bradycardia (less than 50 beats/min) 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.

Cardiac Arrest:

In cardiac arrest, 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.

Adenosine*

Pregnancy Category-C

Schedule H

Indications	*Coronary vasodilator; paroxysmal supraventricular tachycardia; cardiac imaging for coronary artery disease; angina pectoris.*
Availability	**TABLETS** 40, 80 and 120 mg (DT); **INJECTION** 2 ml ampoule (3 mg/ml).

Dose

Oral

40 to 80 mg, 3 to 4 times daily (Max. 480 mg/day).

Rapid intravenous injection (into central or large peripheral vein)

3 mg every 2 seconds with regular cardiac monitoring, if necessary, followed by 6 mg every 1 to 2 min. Increment should not be given if higher level AV block occurs at any particular dose.

Contraindications

Second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted), acute myocardial infarction, cardiovascular shock; asthma.

Precautions

Atrial fibrillation or flutter with accessory pathway (conduction down anomalous pathway may increase); heart transplant; pregnancy (Appendix 7c).

Adverse Effects

Transient facial flush, chest pain, dyspnoea, bronchospasm, choking sensation, nausea, light-headedness; severe bradycardia reported (requiring temporary pacing); ECG may show transient rhythm disturbances; edema; constipation.

Amiodarone*

Pregnancy Category-D

Schedule H

Indications

Severe rhythmic disorder where other therapies cannot be used including tachyarrhythmia associated with Wolff-Parkinson-White syndrome, atrial flutter and fibrillation; all types of paroxysmal tachycardia.

Availability

TABLETS 100 and 200 mg; **INJECTION** 3 ml ampoule (50 mg/ml).

Dose

Oral

200 mg three times a day for one week, reduced to 200 mg twice daily for further one week. Maintenance 200 mg daily or reduced to minimum required to control arrhythmia.

Intravenous infusion
(with central venous catheter).

Initially 5 mg/kg body weight over 20 to 120 min with ECG monitoring, subsequent infusion given if necessary according to response (up to max 1.2g in 24 h).

Contraindications Sinus bradycardia, sino-atrial heart block; unless pacemaker fitted avoid in severe conduction disturbances or sinus node disease; thyroid dysfunction; iodine sensitivity; goitre; avoid intravenous use in severe respiratory failure, circulatory collapse, severe arterial hypotension, avoid bolus injection in congestive heart failure or cardiomyopathy; lactation; pregnancy (Appendix 7c).

Precautions Liver-function and thyroid-function tests required before treatment and then every 6 months; hypokalaemia (measure serum-potassium concentration before treatment); chest x-ray required before treatment; heart failure; elderly; severe bradycardia and conduction disturbances in excessive dosage; intravenous use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) or severe hepatocellular toxicity (monitor transaminases closely); ECG monitoring and resuscitation facilities must be available during intravenous use; porphyria; interactions (Appendix 6d).

Adverse Effects Nausea, vomiting, taste disturbances, raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders), jaundice; bradycardia; pulmonary toxicity (including pneumonitis and fibrosis); tremor, sleep disorders; hypothyroidism, hyperthyroidism; reversible corneal microdeposits (sometimes with night glare); phototoxicity, persistent slate-grey skin discolouration; less commonly onset or worsening of arrhythmia, conduction disturbances, peripheral neuropathy and myopathy (usually reversible on withdrawal); very rarely, chronic liver disease including cirrhosis, sinus arrest, bronchospasm (in patients with severe respiratory failure), ataxia, benign intracranial hypertension, headache, vertigo, epididymo-orchitis, impotence, haemolytic or aplastic anaemia, thrombocytopenia, rash (including exfoliative dermatitis), hypersensitivity including vasculitis, alopecia, impaired vision due to optic neuritis or optic neuropathy (including blindness), anaphylaxis on rapid injection, also hypotension, respiratory distress syndrome, sweating and hot flushes.

Storage Store protected from light at temperature not exceeding 30°C.

Atenolol* (Refer Page No. 281)

Digoxin*

Pregnancy Category-C

Schedule H

Indications

Supraventricular arrhythmias, particularly atrial fibrillation; heart failure.

Availability

TABLET 0.25 mg; **INJECTION** 2 ml (0.5 mg/2 ml); **ELIXIR** 0.05 mg/ml (paediatric use); **SYRUP** 1.5 mg/30 ml.

Dose

Oral

Adult- Atrial fibrillation and heart failure: 1 to 1.5 mg in divided doses over 24 h for rapid digitalization or 250 µg 1 to 2 times daily if digitalization less urgent; maintenance 62.5 to 500 µg daily (higher dose may be divided), according to renal function and heart rate response; usual range 125 to 250 µg daily.

Elderly- Lower dose more appropriate.

Intravenous infusion

Emergency control of atrial fibrillation, over at least 2 h: 0.75 to 1 mg.

Emergency loading dose for heart failure, over at least 2 h: 0.75 to 1 mg.

Note: Infusion dose may need to be reduced if digoxin or other cardiac glycoside given in previous 2 weeks.

Contraindications

Hypertrophic obstructive cardiomyopathy (unless also atrial fibrillation and heart failure); ventricular tachycardia; hypokalaemia; digitalis toxicity; arrhythmias; 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; congestive cardiac myopathy; hypercalcaemia; aortic valve disease, heart block, cardiac dysrrythmias; elderly (reduce dose); renal impairment (Appendix 7d); avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias); lactation; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).

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; sinus bradycardia; apathy; psychosis; malaise.

Storage Tablet: Store protected from light. Injection: Store protected from light in a single dose container. Solution: store protected from light at a temperature not exceeding 30°C.

Diltiazem (Refer Page No. 282)

Esmolol*

Pregnancy Category-C

Indications *Supraventricular arrhythmias (short term treatment); atrial fibrillation; flutter; tachycardia and hypertension in pre-operative period.*

Availability **INJECTION** 10 ml (100 and 250 mg).

Dose ***Intravenous infusion***

Usually with a range of 50 to 200 µg/kg body weight/min under strict professional supervision of cardiologist.

Contraindications Asthma (important: see Bronchospasm below), uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; pheochromocytoma (apart from specific use with alpha-blockers).

The Cardiovascular Society of Medicine has advised that beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

Precautions Avoid abrupt withdrawal especially in ischaemic heart disease, first-degree AV block, portal hypertension (risk of deterioration in liver function); diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked; history of hypersensitivity- may increase sensitivity to allergens and result in more serious hypersensitivity response, also may reduce response to adrenaline (epinephrine); reduce dose of oral propranolol in hepatic impairment; renal impairment; lactation; pregnancy (Appendix 7c); interactions (Appendix 6c).

Adverse Effects Gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders, peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm, dyspnoea; headache, fatigue, sleep disturbances, paraesthesia, dizziness, vertigo, psychoses; sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; rarely, rashes and dry eyes (reversible on withdrawal); on infusion venous irritation and thrombophlebitis; asthenia.

Isoprenaline

Pregnancy Category-C

Schedule H

Indications *Severe bradycardia, unresponsive to atropine; short-term emergency treatment of heart block; ventricular arrhythmias secondary to atrio-ventricular nodal block.*

Availability **TABLETS** 20 mg; **INJECTION** 1 ml ampoule (2 mg/ml).

Dose ***Slow intravenous injection***

2 mg/ml injection under strict professional supervision of cardiologist.

Contraindications Angina pectoris; tachycardia.

Precautions Ischaemic heart disease, diabetes mellitus or hyperthyroidism; pregnancy (Appendix 7c).

Adverse Effects Arrhythmias, hypotension, sweating, tremor, headache, palpitations, tachycardia, nervousness, excitability, insomnia.

Storage Store protected from light at temperature not exceeding 30°C.

Lidocaine (Lignocaine)* (Refer Page No. 417)

Pregnancy Category-B

Indications *Ventricular arrhythmias (especially after myocardial infarction); local anaesthesia.*

Availability **INJECTION** vial 30 ml (1, 2%w/v), 50 ml (21.3 mg/ml); 2%/50 ml; ampoule 5%/2 ml. **JELLY** 2% w/v **OINTMENT** 5% w/v

Dose **Adult-** Ventricular arrhythmias: loading dose of 50 to 100 mg (or 1 to 1.5 mg/kg) at a rate of 25 to 50 mg/min by intravenous injection, followed immediately by intravenous infusion of 1 to 4 mg/min, with ECG monitoring of all patients (reduce infusion dose if required for longer than 24 h).

Note: Following intravenous injection, lidocaine has a short duration of action (of 15 to 20 min). If it cannot be given by intravenous infusion immediately, the initial intravenous injection of 50 to 100 mg can be repeated if necessary once or twice at intervals of not less than 10 min.

Contraindications Sino-atrial disorder; any grade of atrioventricular block or any other type of conduction disturbances, severe myocardial depression, acute porphyria or hypovolaemia, bradycardia, cardiac decompensation.

Precautions Lower dosage in congestive heart failure, bradycardia, ECG monitoring must during therapy, pediatrics; hypotension; renal impairment; porphyria; debilitated patients; hepatic impairment (Appendix 7a); marked hypoxia; severe respiratory depression; following cardiac surgery and in elderly; lactation; interactions (Appendix 6c); pregnancy (Appendix 7c).

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; blurred vision, disorientation.

Storage Store protcted from light.

Mexiletine

Pregnancy Category-C

Schedule H

Indications *Ventricular arrhythmias especially after myocardial infarction.*

Availability **CAPSULES** 50, 100 and 150 mg;
INJECTION 250 mg/10 ml.

Dose ***Oral***

Initial dose; 400 to 600 mg, followed by 200 to 250 mg after 2 h, 3 to 4 times a day.

Intravenous infusion

Slow i.v. infusion of 200 to 250 mg at the rate of 25 mg/min followed by i.v. infusion of 1 mg/min over 1 h.

Contraindications Sinus node dysfunction; hepatic dysfunction; cardiogenic shock, myocardial infarction.

Precautions Hepatic; cardiac or renal failure; hypotension, bradycardia; interactions (Appendix 6d); pregnancy (Appendix 7c).

Adverse Effects Dizziness; confusion; ataxia; bradycardia, hypotension, nausea; vomiting; constipation; palpitations; jaundice; hepatitis; dysarthria.

Storage Store protected from light. Store injection in single dose containers.

Procainamide *

Pregnancy Category-C

Schedule H

Indications *Severe ventricular arrhythmias, especially those resistant to lidocaine or those appearing after myocardial infarction; atrial tachycardia, atrial fibrillation; maintenance of sinus rhythm after cardioversion of atrial fibrillation.*

Availability **TABLET** 250 mg; **INJECTION** 10 ml ampoule/vial (100 mg/ml).

Dose ***Oral***

Adult- Ventricular arrhythmias: up to 50 mg/kg daily in divided doses every 3 to 6 h, preferably controlled by monitoring plasma-procainamide concentration (therapeutic concentration usually within range of 3 to 10 µg/ml).

Atrial arrhythmias: higher doses may be required.

Slow intravenous injection

Ventricular arrhythmias: 100 mg at a rate not exceeding 50 mg/min, with ECG monitoring; may be repeated at 5 min intervals until arrhythmias controlled (max 1g).

Intravenous infusion

0.2 to 1g i.v.; 0.5 to 1g i.m. until oral therapy is possible.

Ventricular arrhythmias: 500 to 600 mg over 25 to 30 min with ECG monitoring, reduced to maintenance dose of 2 to 6 mg/min; if further treatment by mouth required, allow interval of 3 to 4 h after infusion.

Contraindications Asymptomatic ventricular premature contractions; *torsades de pointes;* systemic lupus erythematosus; heart block, heart failure, hypotension; lactation; children; myasthenia gravis.

Precautions Elderly, renal and hepatic impairment (Appendix 7a), asthma, myasthenia gravis; blood dyscrasias; heart failure, cardiomyopathy; cytopenia; digitalis intoxication; electrolyte imbalance; monitor blood count and ECG; pregnancy (Appendix 7c); lactation (Appendix 7b); use only under specialist supervision; interactions (Appendix 6d).

Adverse Effects Nausea, vomiting, diarrhoea, anorexia, rashes, pruritus, urticaria, flushing, fever, myocardial depression, heart failure, angioedema, depression, dizziness, psychosis; blood disorders include leukopenia, haemolytic anaemia and agranulocytosis after prolonged treatment; lupus erythematosus-like syndrome; high plasma procainamide concentration may impair cardiac conduction; hypotension, heart block; hallucinations.

Storage Store protected from light and moisture.

Quinidine

Pregnancy Category-C

Schedule H

Indications *Suppression of supraventricular arrhythmias and ventricular arrhythmias; maintenance of sinus rhythm after cardioversion of atrial fibrillation.*

Availability **TABELTS** 100 and 200 mg.

Dose ***Oral***

Initial test dose of 200 mg to detect hypersensitivity to quinidine.

Adult- Arrhythmias: 200 to 400 mg 3 to 4 times daily; increased if necessary in supraventricular tachycardia to 600 mg every 2 to 4 h (max. 3 to 4g daily); frequent ECG monitoring required.

Contraindications Complete heart block; myasthenia gravis; history of embolism.

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); lactation (Appendix 7b); pregnancy (Appendix 7c).

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.

Storage Store protected from light.

Verapamil* (Refer Page No. 289)

13.3 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 oftten 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 max. 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, 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 drugs.

Beta-adrenoceptor antagonists (beta-blockers) such as atenolol are effective in all grades of hypertension and are particu-

larly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease and heart block.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) such as enalapril 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 effect 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.

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.

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 sulphate is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

Amlodipine*

Pregnancy Category-C

Schedule H

Indications — *Angina, hypertension, coronary artery disease.*

Availability — **TABLETS** 1.25, 2.5, 5, 7.5, 10 and 20 mg.

Dose — ***Oral***

Angina:
Adult- Initially 5 mg once daily, increased if necessary; max. 10 mg once daily.

Hypertension:
Adult- Initially 5 mg once daily, increased if necessary; max. 10 mg once daily.

Elderly- Initial dose- 2.5 mg once daily.

Contraindications — Significant aortic stenosis, sinoatrial node disease, hypersensitivity to dihydropyridines, cardiogenic shock, unstable angina; interactions (Appendix 6d).

Precautions — Hypotension, myocardial infarction, impaired renal function sick-sinus syndrome, severe ventricular dysfunction, hypertrophic cardiomyopathy, severe aortic stenosis, elderly, children, pregnancy (Appendix 7c); lactation; hepatic impairment (Appendix 7a).

Adverse effects — Arrhythmias, postural hypotension; dizziness, ankle edema, hypoesthesia, flatulence, dizziness, blurred vision, facial flushing, dyspnoea, asthenia, muscle cramps, conduction system delay, abdominal pain, headache; sleep disturbances, fatigue.

Storage — Store protected from moisture.

Atenolol* (Refer Page No. 281)

Clonidine (Refer Page No. 546)

Pregnancy Category-C

Schedule H

Indications — *Hypertension of all grades except pheochromocytoma, glaucoma and migraine.*

Availability — **TABLETS** 100 and 150 µg.

Dose — ***Oral***

Adult- 75 to 225 µg/day in two divided doses, increase gradually every two weeks.

Child- Not recommended.

Contraindications Hypersensitivity; sinoarterial node disease, atrioventricular node disease.

Precautions Depressive illness; concurrent antihypertensive therapy, cerebrovascular disease; porphyria; interactions (Appendix 6a, 6c); pregnancy (Appendix 7c).

Adverse Effects Dry mouth; sedation; dizziness; nausea; nocturnal restlessness; occasionally rashes; cardiac arrhythmias; systemic lupus erythmatosus; anxiety; constipation; abdominal pain; hallucination; impotence and depression.

Storage Store injection in a single dose container.

Enalapril*

Pregnancy Category-D

Schedule H

Indications *Heart failure (with a diuretic); prevention of symptomatic heart failure and prevention of coronary ischaemic events in patients with left ventricular dysfunction; hypertension; renal hypertension.*

Availability **TABLETS** 2.5, 5 and 10 mg; **INJECTION** 1 ml ampoule (1.25 mg/ml).

Dose ***Oral***

Adult- Hypertension: initially 5 mg once daily; if used in addition to diuretic.

Heart failure, asymptomatic left ventricular dysfunction: initially 2.5 mg daily under close medical supervision; usual maintenance dose 20 mg daily in 1 to 2 divided doses.

Elderly- Renal impairment: initially 2.5 mg daily. Usual maintenance dose 10 to 20 mg once daily; In severe hypertension may be increased to max. 40 mg once daily.

Contraindications Hypersensitivity to ACE inhibitors (including angioedema), renovascular disease, aortic stenosis; pregnancy (Appendix 7c).

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 7d); liver impairment (Appendix 7a); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); lactation; interactions (Appendix 6a, 6b, 6c); hypervolemia; patients with immunosuppression; hyperkalemia.

Risk of very rapid fall 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 h 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 h after administration or until blood pressure stable.

Avoid enalapril during dialysis with high-flux polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulphate ; also withhold before desensitization with wasp or bee venom.

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; azotemia; acute renal failure; taste disturbances.

Storage

Store protected from light.

Hydralazine

Pregnancy Category-C

Indications

In combination therapy in moderate to severe hypertension, hypertensive crisis; hypertension associated with pregnancy (including pre-eclampsia or eclampsia); heart failure.

Availability

TABLET 25 mg; **INJECTION** 20 mg/ml.

Dose

Oral

Adult- Hypertension: 25 mg twice daily, increased if necessary to max. 50 mg twice daily.

Slow intravenous injection

Adult- Hypertensive crisis (including during pregnancy): 5 to 10 mg diluted with 10 ml Sodium Chloride 0.9%; if necessary may be repeated after 20 to 30 min.

Intravenous infusion

Adult- Hypertensive crisis (including during pregnancy: initially 200 to 300 µg/min; maintenance usually 50 to 150 µg/min.

Contraindications

Idiopathic systemic lupus erythematosus; severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction; cor pulmonale; dissecting aortic aneurysm; porphyria; angina; mitral valvular heart disease; rheumatic disease.

Precautions

Hepatic impairment (Appendix 7a); renal impairment; 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; coronary artery disease; alcohol intake; lactation (Appendix 7b); occasionally over-rapid blood pressure reduction even with low parenteral doses; interactions (Appendix 6b, 6c); pregnancy (Appendix 7c).

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; peripheral neuritis.

Storage Store protected from light at temperature not exceeding 30°C.

Hydrochlorothiazide* (Refer Page No. 397)

Pregnancy Category-B

Indications *Alone in mild hypertension and in combination with other drugs in moderate to severe hypertension; heart failure; oedema; diabetes insipidus.*

Availability **TABLETS** 12.5, 25 and 50 mg.

Dose ***Oral***

Adult- Hypertension: 12.5 to 25 mg daily. Heart failure: initially 25 mg daily on waking up, increasing to 50 mg daily if necessary.

Elderly- Initially 12.5 mg daily for hypertension as well as heart failure.

Contraindications Severe renal or severe hepatic impairment; hyponatraemia; hypercalcaemia; refractory hypokalaemia; symptomatic hyperuricaemia; Addison's disease; gout; diabetes mellitus; persisting hypercalcaemia; anuria; sulphonamide allergy.

Precautions Renal and hepatic impairment (Appendix 7a); lactation (Appendix 7b); elderly (reduce dose); may cause hypokalaemia; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria; severe heart failure; edema; hyperlipidemia; interactions (Appendix 6a, 6b, 6c); pregnancy (Appendix 7c).

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); arrhythmias; hypokalaemia; oliguria; hypomagnesaemia; hyponatraemia; 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); increased heart rate and ventricular ectopic activity.

Losartan*

Pregnancy Category-D

Schedule H

Indications *Congestive heart failure, hypertension (myocardial infarction along with stroke including reduction of stroke risk in hypertension) with left ventricular hypertrophy, diabetic nephropathy in type II diabetes.*

Availability **TABLETS** 25, 50 and 100 mg.

Dose **Hypertension and diabetic nephropathy:**
Adult- 50 mg once daily, increased to 100 mg daily as single dose or in two divided doses, if needed.

Child- ≥ 6 years, initially 700 µg/kg, increased to a max. of 50 mg once daily, if needed.
Elderly over 75 years initially 25 mg daily. Maintenance dose 25 to 100 mg orally in 1 to 2 divided doses.

Contraindications Hyperaldosteronism, hypersensitivity, pregnancy (Appendix 7c), lactation, Not recommended in children <6yrs of age or GFR <30 ml/min/1.73msq.

Precautions Pre-existing heart, liver or kidney diseases, diabetes, lactation, volume depleted patients, renal artery stenosis, monitor serum potassium concentration, elderly, interactions (Appendix 6a).

Adverse effects Abdominal pain, edema, palpitation, back pain, dizziness, sinusitis, upper respiratory tract infection, rash, gastrointestinal disturbances, transient elevation of liver enzymes, impaired renal function, taste disturbances, hyperkalaemia, arthralgia, thrombocytopenia, vasculitis.

Storage Store protected from light and moisture.

Methyldopa*

Pregnancy Category-B

Schedule H

Indications *Hypertension in pregnancy.*

Availability **TABLET** 250 mg.

Dose ***Oral***

Adult- Hypertension in pregnancy: initially 250 mg 2 to 3 times daily; if necessary, gradually increased at intervals of 2 or more days (max 3g daily).

Contraindications Depression; active liver disease; hypersensitivity; therapy with MAO inhibitors; pheochromocytoma; porphyria.

Precautions History of hepatic impairment (Appendix 7a); renal impairment; 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; lactation; pregnancy (Appendix 7c); interactions (Appendix 6b, 6c).

May impair ability to perform skilled tasks; for example operating machinery; driving.

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*

Pregnancy Category-C

Schedule H

Indications — *Hypertension; angina prophylaxis; heart failure; Raynaud's phenomenon.*

Availability — **TABLETS** 5, 10, 20 and 30 mg plain and SR; **CAPSULES** 5, 10, 20 and 30 mg.

Dose — ***Oral***

Adult- Hypertension (as sustained-release tablets): usual range 20 to 100 mg daily in 1 to 2 divided doses.

Contraindications — Cardiogenic shock, advanced aortic stenosis, within 1 month of myocardial infarction, unstable or acute attacks of angina, porphyria; hypersensitivity.

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; monitor drug response in cirrhosis patients; blood pressure monitoring; calcium channel blockers; reduce dose in hepatic impairment; diabetes mellitus; may inhibit labour; lactation (Appendix 7b); pregnancy (Appendix 7c); interactions (Appendix 6b, 6c).

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; exacerbated angina; cardiovascular collapse; ankle swelling; gastrointestinal upset; reversible gingival hyperplasia.

Storage — Store protected from light and moisture.

Propranolol* (Refer Page No. 236 and 287)

Ramipril

Pregnancy Category-D

Schedule H

Indications — *Reduction in risk of myocardial infarction, stroke and death from cardiovascular causes; hypertension; heart failure post myocardial infarction.*

Availability

TABLETS AND CAPSULES 1.25, 2.5, 5 and 10 mg.

Dose

Reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes: Initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg once a day.

Hypertension: The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses.

Heart failure post myocardial infarction: Initial dose is 2.5 mg twice daily, after one week at the starting dose titrate to (if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.

Contraindications

Hypersensitivity to ramipril or any other ACE inhibitor, bilateral renal artery stenosis or a single kidney with unilateral renal artery stenosis.

Precautions

Impaired renal function, impaired liver function, diabetes mellitus (increased risk of hyperkalemia), patients undergoing surgery, history of angioedema; symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy; monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function; administration during pregnancy (Appendix 7c) can cause fetal/neonatal morbidity and death; when pregnancy is detected ACE inhibitors should be discontinued as soon as possible, interactions (Appendix 6a and 6c).

Adverse Effects

Hypotension, cough, asthenia, dizziness, headache, angioneurotic edema, hypersensitivity reactions, erythema multiforme, toxic epidermal necrolysis, Stevens Johnson syndrome, hepatic necrosis, pancreatitis, pancytopenia, thrombocytopenia.

Storage

Store protected from moisture at a temperature not exceeding 30°C.

Sodium Nitroprusside*

Pregnancy Category-C

Schedule H

Indications — *Hypertensive crisis (when treatment by mouth not possible), congestive heart failure.*

Availability — **INJECTION** ampoule/vial 5 ml (50 mg/ml).

Dose — ***Intravenous infusion***

Adult- Hypertensive crisis: initially 0.3 µg/kg/min; usual maintenance dose 0.5 to 6 µg/kg/min; max. dose 8 µg/kg/min; stop infusion if response is unsatisfactory after 10 min at max. dose; lower doses in patients already being treated with antihypertensives.

Contraindications — Compensatory hypertension; severe vitamin B_{12} deficiency; Leber optic atrophy; arterial venous shunting; patients with acute CHF associated with reduced peripheral vascular resistance.

Precautions — Impaired pulmonary function; hypothyroidism; renal impairment; 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 min to avoid rebound effects); pregnancy (Appendix 7c); lactation; interactions (Appendix 6b); hepatic impairment (Appendix 7a).

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; muscle twitching; hypothyroidism; increased anaerobic metabolism.

Adverse effects associated with excessive concentration of cyanide metabolite include tachycardia; sweating; hyperventilation; arrhythmias; marked metabolic acidosis (discontinue infusion and give antidote).

Storage — Store protected from light.

Telmisartan

Pregnancy Category-C

Schedule H

Indications — *Hypertension.*

Availability **TABLETS** 20, 40 and 80 mg.

Dose **Adult**- 40-80 mg once daily.

Contraindications Renal artery stenosis, pregnancy (Appendix 7c), hyperkalemia.

Precautions Interactions (Appendix 6c).

Adverse Effects Cough, angioedema.

Terazosin

Pregnancy Category-C

Schedule H

Indications *Mild to moderate hypertension, benign prostatic hyperplasia.*

Availability **TABLETS** 1, 2 and 5 mg.

Dose

Hypertension:
Adult-Initially 1 mg at bedtime (compliance with bedtime dose is important, see precautions), gradually increase at 7 day intervals. Maintainance dose- 2-10 mg once daily.

Max. 20 mg daily in 1 or 2 divided doses.

Benign prostatic hyperplasia:
Adult- 1 mg at bedtime, gradually increase at 7-day interval. Maintainance dose- 5-10 mg once daily.

Max. 20 mg daily.

Contraindications Hypersensitivity.

Precautions First dose syncope (should be taken just before retiring to bed), kidney disease, liver disease, elderly, pregnancy (Appendix 7c), lactation, interactions (Appendix 6a).

Adverse effects Dizziness, drowsiness, fatigue, dyspnoea, blurred vision, postural hypotension, asthenia, nasal congestion, miosis, chest pain, urinary frequency, weight gain, thrombocytopenia, decreased libido, back pain and pain in extremities.

Storage Store protected from light and moisture.

13.4 Antithrombotic Drugs

Anticoagulants prevent thrombus formation or the extension of an existing thrombus. 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.

Myocardial Infarction:

Management of myocardial infarction includes two phases:

- initial management of the acute attack
- long-term management, including prevention of further attacks

1. Initial Management:

Oxygen 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. Metoclopramide 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 h of infarction (use after 12 h requires specialist advice).

Nitrates may also be given to relieve ischaemic pain.

Early administration of beta-blockers such as atenolol 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 have also been shown to be beneficial in initial management (unless patient has contraindications) when given within 24 h 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 h after infarction. Ventricular fibrillation should be treated immediately with a defibrillator; if this is ineffective alone, the antiarrhythmic drug lidocaine should be given.

All patients should be closely monitored for hyperglycaemia;

those with diabetes mellitus or raised blood-glucose concentration should receive insulin.

2. 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 should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction.

Nitrates may be required for patients with angina.

The use of statins 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 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.

Abciximab

Pregnancy Category-C

Schedule H

Indications — *Patients undergoing percutaneous coronary interventions.*

Availability — **INJECTION** 5 ml vial (2 mg/ml).

Dose — 0.25 mg/kg bolus followed by infusion of 0.125 µg/kg per min (maximum 10 µg/min) for 12 to 24 h.

Contraindications — Surgery within 10 days, including organ biopsy, puncture of noncompressible vessels, serious trauma, cardiopulmonary resuscitation, active bleeding, serious gastrointestinal bleeding within 3 months, previous cerebrovascular accident or active intracranial process, thrombocytopenia, severe uncontrolled hypertension, aortic dissection, acute pericarditis.

Precautions — Monitor platelet count for thrombocytopenia; interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects — Bleeding, thrombocytopenia.

Storage — Store between 2-8°C, do not freeze.

Acetylsalicylic Acid* (Refer Page No. 4, 239 and 281)

Pregnancy Category-D

Indications — *Prophylaxis of cerebrovascular disease or myocardial infarction; pyrexia, pain, inflammation; arterial thromboembolism prophylaxis.*

Dose — ***Oral***

Adult- Prophylaxis of cerebrovascular disease or myocardial infarction: 75 to 100 mg daily.

Contraindications — Hypersensitivity (including asthma; angioedema; urticaria or rhinitis) to acetylsalicylic acid or any other NSAID; children and adolescents under 16 years (Reye's syndrome); active peptic ulceration; haemophilia and other bleeding disorders; hypoprothrombinemia.

Precautions Asthma; uncontrolled hypertension; history of blood coagulation defects; lactation (Appendix 7b); interactions (Appendix 6a, 6c, 6d), pregnancy (Appendix 7c), hepatic impairment and renal impairment (Appendix 7a and 7d).

Adverse Effects Bronchospasm;gastrointestinalhaemorrhage (rarely, major); also other haemorrhage (for example subconjunctival); urticaria; hepatomegaly.

Alteplase

Pregnancy Category-C

Schedule H

Indications *Acute myocardial infarction, acute massive pulmonary embolism, acute ischaemic stroke.*

Availability **INJECTION** 20 and 50 mg/vial.

Dose ***Intravenous***

Acute myocardial infarction
Adult: The recommended total dose is 100 mg. Administer as soon as possible after the onset of symptoms.
Accelerated infusion (1.5 h): Max 100 mg; as a 15 mg intravenous bolus, followed by 50 mg infused over the next 30 minutes, and then 35 mg infused over the next 60 minutes. Patients <67 kg: total dose should be ≤1.5 mg/kg; 15 mg as i.v bolus, then 0.75 mg/kg (up to a max of 50 mg) to be infused over 30 minutes, and then 0.50 mg/kg over the next 60 minutes not to exceed 35 mg.
3-Hour Infusion: Max 100 mg; 60 mg in the first hour (of which 6 to 10 mg is administered as a bolus) then 20 mg/h for 2 h. For patients < 65 kg, 0.75 mg/kg in 1st hour (including 0.045-0.075 mg/kg bolus in first 1-2 minutes), then 0.25 mg/kg/h x 2 hours.
Acute massive pulmonary embolism
Adult: 100 mg (not >1.5 mg/kg for patients weighing < 65 kg).
First 10 mg as bolus followed by infusion of the remainder dose over 2 hours.
Heparin therapy to be instituted or reinstituted near the end of or immediately following the alteplase infusion when the partial thromboplastin time returns to twice normal or less.
Acute ischemic stroke
Adult: Use recommended within first 3 h of onset of the symptoms. Infuse 0.9 mg/kg (up to a max. of 90 mg) over 60 minutes with 10% of the dose as bolus over the first minute.

Contraindications Uncontrolled hypertension with possible cerebrovascular haemorrhage, recent surgery or trauma, susceptibility to internal bleeding, uncontrolled hypertension, esophageal varices, heavy vaginal bleeding, bleeding diathesis, active peptic ulceration.

Precautions Monitor for bleeding and BP in acute stroke.
Caution in recent surgery or invasive procedures, diabetic hemorrhagic retinopathy, severe hepatic and renal impairment, pregnancy (Appendix 7c), lactation, children, elderly, interactions (Appendix 6c).

Adverse Effects Hemorrhage including intracranial, gastrointestinal or genitourinary bleeding, transient hypotension, reperfusion dysrythmias, cerebral edema, seizures, allergic-type reactions, nausea, vomiting.

Storage Store protected from heat, light and moisture at room temperature (<30°C) or under refrigeration. Use reconstituted solution within 8 hours.

Clopidogrel*

Pregnancy Category-B

Schedule H

Indications *Prophylaxis in thromboembolic disorders including myocardial infarction, peripheral arterial disease and stroke, acute coronary syndrome.*

Availability **TABLETS** 75 and 150 mg.

Dose **Adult-** 75 mg once daily.

Non-ST segment elevation myocardial infarction: loading dose 300 mg followed by 75 mg once daily.

Contraindications Hypersensitivity, active pathological bleeding such as peptic ulcer or intracranial hemorrhage, coagulation disorders, lactation.

Precautions Patient with increased risk of bleeding from trauma, surgery or other pathological conditions, ulcers, renal impairment, hepatic impairment, history of bleeding or haemostatic disorder, pregnancy (Appendix 7c); interactions (Appendix 6c).

Adverse Effects Bleeding, neutropenia, thrombocytopenia, other bone marrow toxicity, diarrhoea, epigastric pain, rashes, paraesthesia, vertigo.

Heparin* (Refer Page No. 331)

Streptokinase*

Pregnancy Category-C

Schedule H

Indications *Life-threatening deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism; thrombosed arteriovenous shunts; acute myocardial infarction.*

Availability **INJECTION** (Powder for solution for injection) 7,50,000 and 15,00,000 units vial.

Dose ***Intravenous infusion.***

Adult- Thrombosis: 2,50,000 units over 30 min, followed by 1,00,000 units every h for 12 to 72 h according to condition with monitoring of clotting parameters.

Myocardial infarction: 15,00,000 units over 60 min.

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; pregnancy (Appendix 7c).

Precautions Risk of bleeding from any invasive procedure; including injection; external chest compression; 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; platelet count; fibrinogen level; thrombin and prothrombin time.

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.

Storage Store in a sealed container protected from light in refrigerator (2 to 8°C). The container should be sterile and sealed so as to exclude micro-organisms. Under these conditions the contents may be expected to retain potency for 2 years.

Urokinase*

Pregnancy Category-C

Schedule H

Indications *Acute myocardial infarction; pulmonary embolism; deep vein thrombosis; peripheral vascular thrombosis; peripheral arterial thromboembolism; arterial thrombosis.*

Availability **INJECTION** 20,000, 50,000, 2,50,000, 5,00,000, 7,50,000 and 10,00,000 IU/vial.

Dose ***Intravenous infusion***

Deep vein thrombosis: 4,400 units/kg body weight in 15 ml Sodium Chloride (0.9%w/v) over 10 min followed by 4,400 units/kg body weight for 12 to 24 h.

Pulmonary embolism: 4,400 units/kg body weight in 15 ml Sodium Chloride (0.9%w/v) over 10 min followed by 4,400 units/kg body weight for 12 to 24 h, alternatively 15,000 units/kg body weight directly into the pulmonary artery initially, subsequent doses adjusted according to response, max. 3 doses in 24 h.

Contraindications In recent haemorrhage; trauma; or surgery (including dental extraction); coagulation defects; bleeding diatheses; aortic dissection; coma; history of cerebrovascular disease especially recent events or with any residual disability; recent symptoms of possible peptic ulceration; heavy vaginal bleeding; severe hypertension; active pulmonary disease with cavitation; acute pancreatitis; pericarditis; bacterial endocarditis; severe liver disease and oesophageal varices.

Precautions

Should be used with caution if there is a risk of bleeding including that from venepuncture or invasive procedures. They should also be used with caution in external chest compression; pregnancy (Appendix 7c); elderly; hypertension; abdominal aneurysm or other conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation); diabetic retinopathy (very small risk of retinal bleeding) and recent or concurrent use of drugs that increase the risk of bleeding; hematocrit platelet count; thrombin and prothrombin time.

Adverse Effects

Nausea; vomiting and bleeding. When used in myocardial infarction, reperfusion arrhythmias may occur. Hypotension can also occur and can usually be controlled by elevating the patient's legs or by reducing the rate of infusion or stopping it temporarily. Back pain; fever and convulsions have been reported. Bleeding is usually limited to the site of injection; but intracerebral haemorrhage or bleeding from other sites can occur. Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (aprotinin or tranexamic acid). Rarely, further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli). It causes allergic reactions (including rash; flushing and uveitis) and anaphylaxis has also been reported.

Storage

Store in a sealed container protected from light in refrigerator (2 to 8^{o}C). The container should be sterile, tamper evident and sealed so as to exclude micro-organisms.

13.5 Blood Products and Plasma Substitutes

13.5.1 Plasma Substitutes

Dextran 70 and polygeline are macromolecular substances which are metabolized slowly; they may be used to expand and maintain blood volume in shock arising from conditions such as burns or septicaemia. 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*

Pregnancy Category-C

Indications	*Burns, hypoproteinaemia, shock, hypovolemia, acute liver failure, dialysis.*
Availability	**SOLUTION** 5%, 10%, 20%.
Dose	***Intravenous infusion***
	For hypovolemia: **Adult-** 25g,
	Child- 1g/kg.
	Max.- 2g of 20%/kg body weight.
	For hypoproteinaemia: **Adult-** 2g/kg daily.
	Usual rates of infusion: up to 5 ml/min (5%) or 1 to 2 ml/min (20%).
Contraindications	Congestive heart failure, severe anaemia, history of allergic reactions to human albumin; pregnancy (Appendix 7c).

Precautions If dehydration is present additional fluid must follow the administration of albumin. Administration of albumin should be supplemented or replaced by packed red blood cells, **history of cardiac or circulatory disease, increased capillary permeability.**

Adverse effects Allergic (or) pyrogenic reactions, tachycardia, rash, anaphylactic shock, increased salivation.

Storage Store protected from light at a tempreture between 2-25^{o}C. Human albumin stored at 2-8^{o}C may be expected to continue to meet the requirements of the monograph for five years from the date on which it was heated at at 60^{o}C for 10 hours. Human albumin stored at a temperature not exceeding 25^{o}C may be expected to meet the requirements of the monograph for three years from the date on which it was heated at 60^{o}C for 10 hours.

Dextran 40*

Pregnancy Category-C

Schedule H

Indications *Plasma volume expansion during hypovolemic shock when blood not available, Prophylaxis of thromboembolic disorders to improve local circulation in peripheral vascular occlusion.*

Availability **INFUSION** 10% dextran 40 + 5% dextrose or 0.9% sodium chloride.

Dose ***Intravenous***

To improve local circulation in peripheral vascular occlusion: Adult- 500-1000 ml (10-20 ml/kg) in first 24 hours; thereafter 500 ml every 1-2 days for up to 2 weeks.
Thromboembolism prophylaxis: Adult- 500-1000 ml (10-20 ml/kg) on day of surgery, then 500 ml daily for 2-3 days, then 500 ml every second or third day, for up to 2 weeks.
Shock: Adult- initially 500-1000 ml (10-20 ml/kg) infused as rapidly as needed; may follow with 500 ml (10 ml/kg) during the same 24 hour period; thereafter 500 ml (10 ml/kg) may be repeated daily for up to 5 days.

Contraindications Hypersensitivity, cardiac decompensation, oliguria or anuria, hemostatic defects, thrombocytopenia, blood coagulation disorder, pulmonary oedema, neonates.

Precautions Renal and hepatic impairment, pregnancy (Appendix 7c), lactaion, diabetes, cardiac patients, elderly, monitor urine output, monitor for signs of circulatory overload, interactions (Appendix 6c).

Adverse Effects Nausea, vomiting, local injection site reaction, hypersensitivity and anaphylactoid reactions, increased serum SGOT and SGPT concentrations, osmotic nephrosis.

Storage Store protected from light at a temperature not exceeding 30^{o}C.

Hydroxy Ethyl Starch*

Pregnancy Category-C

Indications *Therapy for hypovolaemia, shock in surgery, trauma and infection to improve haemodynamics, macrocirculation, microcirculation and oxygen supply; improve organ function in blood loss.*

Availability **INFUSION** 300 and 500 ml.

Dose ***Intravenous infusion***

500 to 1000 ml (daily max. 1500 ml).

Contraindications Renal failure; haemorrhage; coagulation disorders; anuria; oligouria.

Precautions Should be used with caution in patients with cardiac disease; liver disease; or renal impairment; urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25-30% and the patient should be monitored for hypersensitivity reactions; bleeding disorder; sufficient fluid should be administered to avoid dehydration; pregnancy (Appendix 7c).

Adverse Effects Hypersensitivity reactions may occur including; rarely,; severe anaphylactoid reactions; transient increase in bleeding time may occur; headache; tachycardia; itching; fall in blood pressure.

13.5.2 Plasma Fraction 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 deficencies 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 IX Complex (Coagulation Factors II, VII, IX, X) Concentrate*

Pregnancy Category-C

Indications	*Replacement therapy for factor IX deficiency in haemophilia; bleeding due to deficiencies of factors II, VII or X.*
Availability	**INFUSION** (Powder for solution for infusion), factor II, VII, IX and X 500 to1500 units.
Dose	***Slow intravenous infusion*** **Adult and child-** Haemophilia B: according to patient's needs. Treatment of bleeding due to deficiencies in factor II, VII or X as well as IX: according to patient's need.
Contraindications	Disseminated intravascular coagulation; hypersensitivity to any component of the product.
Precautions	Risk of thrombosis (probably less risk with highly purified preparations); pregnancy (Appendix 7c); preexisting disease; check heart rate; interactions (Appendix 6c).
Adverse Effects	Allergic reactions including chills; fever; hepatitis; pulmonary embolism; disseminated intravascular coagulation.
Storage	Store protected from light.

Factor VIII Concentrate*

Pregnancy Category-C

Indications *Control of haemorrhage in haemophilia A.*

Availability **INFUSION** (Powder for solution for infusion), factor VIII 250 to 1500 units.

Dose ***Slow intravenous infusion***

Adult and child- Haemophilia A; according to patient's needs.

Contraindications Hypersensitivity to any component of the product.

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); pregnancy (Appendix 7c); check heart rate.

Adverse Effects Allergic reactions including chills; fever; hepatitis; anaphylaxis; fulminating hepatitis.

Storage Store protected from light.

Tranexamic Acid

Pregnancy Category-C

Schedule H

Indications *Prevention of hemorrhage due to dental procedures in hemophilics, cyclic heavy menstrual bleeding, hereditary angioedema, cone biopsy, epistaxis, traumatic hyphema.*

Availability **TABLETS-** 250 mg, 500 mg and 1g.
INJECTION- 100 mg/ml, 500 mg/5 ml.

Dose **Dental extraction in Hemophilics:** Immediately before tooth extraction, 10 mg/kg intravenously.
Following tooth extraction, intravenous therapy, at a dose of 10 mg/kg body weight three to four times daily, may be used for 2 to 8 days.
Menorrhagia: 1300 mg orally 3 times daily up to 5 days during menstruation.
Cone biopsy: 1000-1500 mg 2-3 times daily for 12 days postop eratively.
Epistaxis: 1000 mg 3 times daily for 7 days.
Hyphema: 1000-1500 mg 2-3 times daily for 7 days.
Hereditary angioedema: 1000-1500 mg 2-3 times daily.

Contraindications Hypersensitivity, acquired defective colour vision, subarachnoid hemorrhage, active intravascular clotting, pregnancy (Appendix 7c), interactions (Appendix 6c).

Precautions

Renal impairment, disseminated intravascular coagulation, thromboembolic history, coadministration with hormonal contraceptives may increase risk of thrombosis, stroke, or myocardial infarction; women using hormonal contraception should take tranexamic acid only if there is a strong medical need, and if the benefit of treatment outweighs risks. Ligneous conjunctivitis has been reported. Retinal venous and arterial occlusion has been reported in patients using tranexamic acid. Patients should be instructed to report visual and ocular symptoms promptly.

Adverse Effects

Nausea, vomiting, diarhoea, disturbances in colour vision (discontinue), thromboembolic events, allergic skin reactions; giddiness and hypotension on rapid intravenous injection, headache, backache, musculoskeletal pain.

Storage

Store protected from light and moisture at a temperature not exceeding 30^{o}C.

13.6 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 sulphate is a specific antidote.

Oral anticoagulants take at least 48-72 h 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 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.

Heparin*

Pregnancy Category-C

Schedule H

Indications

Treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism; atrial fibrillation with embolism; treatment and prophylaxis of peripheral arterial embolism; prophylaxis of deep vein thrombosis in major surgery; lipemia clearing.

Availability

INJECTION vials 1000, 5000 and 25,000 IU/ml.

Dose

Intravenous injection

Adult-Treatment of deep-vein thrombosis and pulmonary embolism: loading dose of 5000 units (10,000 units in severe pulmonary embolism) followed by continuous intravenous infusion of 15 to 25 units/kg/h.
Child- 50 to 100U/kg every 4 to 6 h.

Subcutaneous injection

15,000 units every 12 h; laboratory monitoring is essential, preferably on a daily basis and dose adjusted accordingly.

Prophylaxis in general surgery: 5,000 units 2 h before surgery, then every 8 to 12 h for 7 days or until patient is ambulant (monitoring not needed); during pregnancy (with monitoring) 5,000-10,000 units every 12 h.

Note: Not intended to cover prosthetic heart valve management in pregnancy, which requires specialist management.

Child- 250 units/kg every 12 h.

Intravenous injection and continuous intravenous infusion.

Child- By intravenous injection: lower loading dose, then by continuous intravenous infusion; 15 to 25 units/kg/h.

Contraindications Hypersensitivity to heparin; haemophilia and other haemorrhagic disorders; thrombocytopenia; peptic ulcer; recent cerebral haemorrhage; severe hypertension; severe liver or renal disease; after major trauma or recent surgery (especially to eye or nervous system); threatened abortion; piles; bacterial endocarditis; large malignancies; tuberculosis; lumbar puncture; chronic alcoholics; acetylsalicylic acid and other antiplatelet drugs.

Precautions Hepatic impairment (Appendix 7a) and renal failure; hypersensitivity to low molecular weight heparins; spinal or epidural anaesthesia-risk of spinal haematoma; diabetes mellitus; acidosis; concomitant potassium-sparing drugs-increased risk of hyperkalaemia; lactation; paediatrics; elderly; interactions (Appendix 6c); pregnancy (Appendix 7c).

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; bleeding due to overdose.

Storage Store at a temperature not exceeding 30°C.

Menadione Sodium Sulphate

(Refer Phytomenadione below)

Phytomenadione*

Pregnancy Category-C

Schedule H

Indications *Antagonist to warfarin; prophylaxis against haemorrhagic disease of the newborn; vit K deficiency, hematuria, menorrhagia.*

Availability **TABLETS** 5 and 10 mg; **INJECTION** 10 mg/ml.

Dose ***Slow intravenous injection***

Adult- Warfarin-induced hypoprothrombinaemia, no bleeding or minor bleeding: 500 µg.

Oral

For vitamin K deficiency: 10 to 40 mg daily.

Warfarin-induced hypoprothrombinaemia, no bleeding or minor bleeding: 5 mg.

Oral or intramuscular injection

Less severe haemorrhage: 10 to 20 mg.

Slow intravenous injection

Severe haemorrhage: 2.5 to 5 mg; very rarely, up to 50 mg (but risk of over correction with high dosage).

Intravenous or intramuscular injection

Child- Neonates: Haemorrhagic disease of the newborn (treatment): 1 mg with further doses if necessary at 8 h intervals (prophylaxis).

Intramuscular injection

Child- 0.5 to 1 mg as single dose.

Oral

Child- 2 mg followed by a second dose after 4 to 7 days and for breastfed babies a third dose after 1 month.

Contraindications Hypersensitivity.

Precautions Reduce dose in elderly; hepatic impairment; not an antidote to heparin; can cause haemolysis in patients with G-6-PD; increased risk of severe haemolytic anaemia in neonates after large doses; premature neonates weighing < 2.5 kg; pregnancy (Appendix 7c).

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.

Storage Store protected from light.

Protamine*

Pregnancy Category-C

Indications *Antidote to overdosage with heparin; antidote for heparin in controlled bleeding.*

Availability **SOLUTION** 5 ml (1%); **INJECTION** 5 ml ampoule (10 mg/ml).

Dose

Intravenous injection

Heparin overdose, over approximately 10 min; 1 mg neutralizes 80 to 100 units heparin when given within 15 min, if longer time, less protamine needed as heparin is rapidly excreted. 1 ml neutralises the effect of 1000 ml i.u. of circulating heparin; max. single dose 50 mg (5 ml).

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; pregnancy (Appendix 7c); lactation; children.

Adverse Effects

Nausea; vomiting; lassitude; flushing; hypotension; bradycardia; dyspnoea; allergic reactions (including angioedema; anaphylaxis); allergy specially if previous exposure to protamine insulin; fish allergy; infertile or vasectomised men.

Storage

Store protected from light in a single dose container.

Warfarin*

Pregnancy Category-X

Schedule H

Indications

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks; myocardial infarction; vulvular heart disease.

Availability

TABLETS 1, 2 and 5 mg.

Dose

Oral

Adult- Prophylaxis and treatment of thromboembolic disorders; 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 to 9 mg administered at the same time each day.

Given as slow injection over 1 to 2 minutes into peripheral vein, initially 5 mg daily.
For rapid anticoagulation: initially 10 mg daily for 2 days, maintenance dose 2 to 10 mg daily.

Note: Wherever possible, the base-line prothrombin time should be determined before the initial dose is given.

Contraindications Pregnancy (Appendix 7c); peptic ulcer; severe hypertension; bacterial endocarditis; hypersensitivity; blood dyscrasias; recent surgery; psychosis; pericardial effusion; cerebrovascular disorder; alcoholism; senility; aneurysm.

Precautions Heparin induced thrombocytopenia; surgery or trauma; Vit C, K; lactation; alcoholics; purple toes syndrome; discontinue if necrosis develops; elderly; hepatic impairment (Appendix 7a) or renal failure; recent surgery; lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6c, 6d).

Adverse Effects Haemorrhage; hypersensitivity; rash; alopecia; diarrhoea; unexplained drop in haematocrit; 'purple toes'; skin necrosis; jaundice; hepatic dysfunction; nausea; vomiting and pancreatitis.

Storage Store protected from light.

13.7 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, β-blockers (metoprolol, carvedilol and bisoprolol), 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 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 is required. In severe fluid retention, intravenous furosemide produces relief from 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 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 sympto-

matic 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 produces mainly venous dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea. Hydralazine 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 µg/kg per min) cause vasoconstriction, with a worsening of heart failure.

Digoxin* (Refer Page No. 295)

Dobutamine*

Pregnancy Category-B

Schedule H

Indications	*Acute heart failure; acute myocardial infarction; cardiogenic shock following cardiac surgery; specific shock; acute decompensation of chronic CHF.*
Availability	**INJECTION** 250 mg/20 ml, 40 mg/ml, 12.5 mg/ml, 5 ml ampoule (50 mg/ml), vial 250 mg/20 ml, 50 mg/4 ml; 250 mg dry sterile lyophilised powder.
Dose	2.5 to 10 µg/kg/min which can be titrated to 40 µg/kg/min as per the individual requirement.
Contraindications	Hypersensitivity; idiopathic hypertrophic subaortic stenosis.
Precautions	Interactions (Appendix 6c); pregnancy (Appendix 7c); monitor heart rate and rhythm; arterial BP and infusion rate closely; correct hypovolemia prior to treatment; elderly; neonates; risk of rapid ventricular response in patients with atrial fibrillation; children.
Adverse Effects	Tachycardia and marked increase in systolic blood pressure indicate overdosage; phlebitis; rarely, thrombocytopenia.

Storage Store protected from light.

Dopamine*

Pregnancy Category-C

Schedule H

Indications *Cardiogenic shock in myocardial infarction or cardiac surgery; acute heart failure.*

Availability **INJECTIONS** 5 ml vial (40 mg/ml), 5 and 10 ml ampoule (200 mg/5 ml).

Dose ***Intravenous infusion***

Adult- Cardiogenic shock: into large vein, initially 2 to 5 µg/kg/min; gradually increased by 5 to 10 µg/kg/min according to blood pressure, cardiac output and urine output; seriously ill patients up to 20 to 50 µg/kg/min. By intravenous route initially 1 to 5 µg/kg/min can be increased gradually to 5 to 10 µg/kg/min. max 20 to 50 µg/kg/min in serious patients.

Contraindications Hypersensitivity; tachyarrhythmias, ventricular fibrillation, ischaemic heart disease; pheochromocytoma; 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 6c); history of atherosclerosis; Raynaud's disease; diabetic endocarditis; dispropotionate increase in diastolic pressure; pregnancy (Appendix 7c); lactation; paediatrics. Dopamine must be diluted before i.v. administration.

Adverse Effects Nausea and vomiting; peripheral vasoconstriction; hypotension with dizziness; fainting; flushing; tachycardia; ectopic beats; palpitations; anginal pain; headache; dyspnoea; hypertension particularly in overdosage.

Storage Store in an airtight container protected from light.

Enalapril* (Refer Page No. 305)

Furosemide* (Refer Page No. 397)

Pregnancy Category-C

Indications *Oedema; mild to moderate hypertension.*

Availability **TABLETS** 40, 100 and 500 mg; **INJECTION** ampoule 20 mg/ml, 10 mg/2 ml, 250 mg/25 ml, 20 mg/2 ml.

Dose ***Oral***

Adult- Oedema: initially 40 mg daily on waking up. Maintenance. 20 to 40 mg daily; may be increased to 80 mg daily or more in resistant oedema: max 600 mg daily in severe cases.

Child- 1 to 3 mg/kg daily (max. 40 mg daily).

Slow intravenous injection

Adult- Acute pulmonary oedema: 20 to 50 mg, if necessary increase by 20 mg step-by-step every 2 h; if effective single dose is more than 50 mg, at a rate not exceeding 4 mg/min.

Child- 0.5 to 1.5 mg/kg daily (max. 20 mg daily).

Slow intravenous infusion

Adult- Oliguria (glomerular filtration rate less than 20 ml/min): at a rate not exceeding 4 mg/min, initially 250 mg over 1 h.

If urine output not satisfactory during the h after first dose, infuse 500 mg over 2 h then; if no satisfactory response is there in an h after second dose, infuse 1g over 4 h.

If no response is there after third dose, dialysis is probably necessary.

Contraindications Renal failure with anuria; precomatose states associated with liver cirrhosis; severe sodium and water depletion; hypersensitivity to sulphonamides and furosemide; hypokalaemia; addison's disease; lactation.

Precautions Monitor electrolytes particularly potassium and Sodium; hypotension; elderly (reduce dose); pregnancy (Appendix 7c); lactation; correct hypovolaemia before using in oliguria; renal impairment; hepatic impairment (Appendix 7a); prostatic enlargement; porphyria; interactions (Appendix 6b, 6c); gout; impaired micturition; infusion rate should not exceed 4 mg/min to reduce the risk of ototoxicity; monitor serum levels for calcium or magnesium (may be lowered).

Adverse Effects Hypokalaemia; hypomagnesaemia; hyponatraemia; hypochloraemic 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); gastrointestinal upset; malaise; blood dyscrasias; vertigo; orthostatic hypotension; jaundice; tinnitus; renal calcification in premature infants.

Storage Store protected from light.

Hydrochlorothiazide* (Refer Page No. 308 and 397)

Spironolactone* (Refer Page No. 399)

13.8 Lipid Lowering Drugs

Drug therapy to lower plasma lipids should be used in addition to dietary management and correction of other modifiable cardiovascular risk factors. Studies indicate that, 1% drop in serum cholesterol reduces the risk for Coronary heart disease (CHD) by 2%.

Various classes of drugs used as lipid lowering drugs are-

H mg-CoA reductase inhibitors

They are the most efficacious and tolerable drugs like simvastatin, pravastatin, atorvastatin etc. They are primarily indicated in secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease following acute myocardial infarction or stroke and in primary prevention of arterial disease in patients who are at high risk because of elevated serum cholesterol concentration. Common adverse effects include mild gastrointestinal disturbances, rhabdomyolysis etc.

Fibric acid derivatives

This class of drugs including fenofibrate, gemfibrozil etc are indicated in patients with mixed dyslipidemia (i.e. raised serum triglycerides and cholesterol), low high density lipoprotein (HDL) and high risk of atheromatous disease (often type 2 diabetic patients), and in severe treatment- resistant dyslipidemia. Major adverse effect include rhabdomyolysis and myoglobulinuria. Fibrates are better avoided in alcoholics.

Bile acid sequestrants

Drugs like cholestyramine, colestipol though are not clinically popular because of interference with absorption of many drugs like digoxin, warfarin etc and poor patient acceptability, but can be indicated in heterozygous familiar hypercholesterolemia. Adverse effects include nausea, abdominal bloating, constipation or diarrhoea.

Nicotinic acid

Nicotinic acid reduces serum cholesterol and triglycerides levels in types II, III, IV, and V hyperlipoproteinemias. Adverse effects include flushing, palpitations and gastrointestinal tract disturbances.

Atorvastatin*

Pregnancy Category-X

Schedule H

Indications — *Primary and secondary hypercholesterolemia, prevention of cerebrovascular accidents, primary prevention of coronary heart disease.*

Availability — **TABLETS** 5, 10, 20, 40 and 80 mg.

Dose — ***Oral***

Adult- 10 mg daily, increased at 4 weeks interval. Max dose 80 mg.

Contraindications — Hypersensitivity; active liver diseases or unexplained persistent elevation of serum transaminase; pregnancy (Appendix 7c), lactation.

Precautions — Patients who consume substantial quantities of alcohol and have a history of liver diseases, Children below 10 years, premenarcheal females; interactions (Appendix 6a, 6c).

Adverse Effects — Myopathy is the serious adverse effect; headache; infrequent elevation of creatinine phosphokinase; rhabdomyolysis; insomnia; dizziness; abdominal pain, constipation, diarrhoea, dyspepsia, flatulence and nausea.

Storage — Store protected from moisture at a tempreture not exceeding 30^{o}C.

Ezetimibe

Pregnancy Category-C

Indications — *Hypercholesterolemia, hyperlipidaemias, homozygous familial sitosterolaemia.*

Availability — **TABLETS** 10 mg.

Dose — **Adult-** 10 mg once daily.
10-18 years: 10 mg once daily.

Contraindications — Hypersensitivity, children below 10 years, pregnancy (Appendix 7c), interactions (Appendix 6c, 6d), lactation, moderate to severe liver disease or unexplained serum transaminase elevation, acute pancreatitis.

Precautions — Renal or mild hepatic impairment, immediately discontinue ezetimibe and any H mg-CoA reductase inhibitor or fibrates if myopathy is diagnosed.

Adverse Effects Diarrhoea, sinusitis, pharyngitis, cough, arthralgia, myalgia, respiratory infection and fatigue, hepatitis/increased serum transaminases, increased creatinine phosphokinase, myopathy/rhabdomyolysis, headache, nausea, rash, dizziness, chest pain, abdominal pain with cramps, back pain, biliary calculus, thrombocytopenia.

Storage Store protected from light and moisture at a temperature not exceeding 30°C

Fenofibrate

Pregnancy Category-C

Schedule H

Indications *Hypercholesterolemia, hypertriglyceridemia.*

Availability **CAPSULES** 67 and 200 mg, **TABLETS** 145 and 160 mg **INJECTIONS** 20, 40 and 60 mg/vial.

Dose **Hyperlipidemia:**
Adult- Initial dose 67 mg 2-4 times a day (micronized) or 200 mg/day in divided doses (non-micronized).

Child- 5 mg/kg daily.

Contraindications Hypersensitivity, severe renal and hepatic impairment, preexisting gall bladder disease, primary biliary cirrhosis, pregnancy (Appendix 7c), lactation.

Precautions Pancreatitis; skeletal muscle effects; renal and hepatic impairement; monitor for LFT and blood counts regularly; interactions (Appendix 6c).

Adverse Effects Myalgia; hepatitis; rashes; cholelithiasis, rhabdomyolysis; increased SGPT and SGOT, abdominal pain, photosensitivity; rhinitis; sinusitis.

Storage Store protected from light.

Nicotinic acid

Pregnancy Category-C

Schedule H

Indications *High risk hyperlipidaemia, nicotinic acid deficiency, peripheral vascular disease.*

Availability **Tablets** 375 and 500 mg Plain and 375 mg SR.

Dose ***Oral***

Treatment and prophylaxis of nicotinic acid deficiency: Adult- 500 mg daily.
Hyperlipidaemia: Adult- 1-2 g, two to three times daily, maximum dose- 6 g per day; (As extended release tablets max. dose is 2 g). Niacin should be started at low doses and increased slowly over several weeks.
Peripheral vascular disease: Adult- 100-150 mg, three to five times daily; (Extended release preparation-) 300-400 mg 12 hourly.

Contraindications Hypersensitivity, liver disease, severe hypotension, diabetes, arterial bleeding.

Precautions Gout, hepatic dysfunction, children, pregnancy (Appendix 7c), lactation, myasthenia gravis, interactions (Appendix 6a and 6c).

Adverse Effects Headache, diarrhoea, vomiting, fainting, peptic ulcer, hyperuricaemia, gout, toxic amblyopia, flushing, hyperpigmentation, dry skin, muscle pain, jaundice, pruritus, atrial fibrillation. Flushing can be blocked by administering 300 mg of aspirin half an hour before taking niacin, or by taking one tablet of ibuprofen per day.

Storage Store protected from heat and moisture at room temperature.

23. Drugs for Respiratory Diseases

23.1 Antiasthmatics and Drugs for Chronic Obstructive Pulmonary Disease (COPD)

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 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. Antiasthmatics 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 inhalation, oral and parenteral (subcutaneous, intramuscular or intravenous routes). 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 fir mly 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 inhalers 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 min 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 β_2-agonists, corticosteroids and theophylline.

Parenteral:

Drugs such as corticosteroids, aminophylline etc. 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/min) 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). Patients should also be given salbutamol or terbutaline via a nebulizer. In emergencies where a nebulizer is not available, salbutamol 100 µg 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 intravenously; for children, prednisolone 1-2 mg/kg by mouth (1-4 years, max. 20 mg, 5-15 years, max. 40 mg) or hydrocortisone 100 mg 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 β_2-agonist; both cause more adverse effects than nebulized β_2-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) in asthma has generally been superseded by β_2-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 Childrens under 5 Years

Preferred treatments are in bold print

	Long-term Preventive	**Quick Relief**
STEP 4 Severe Persistent	Daily medications • Inhaled corticosteroid, beclomethasone dipropionate MDI with spacer and face mask > 1 mg daily or nebulized beclomethasone > 1 mg twice daily. Consider short course of soluble prednisolone tablets, regular inhaled long-acting β_2-agonist or modified-release theophylline. Also, nebulized β_2-agonist.	• Inhaled short-acting bronchodilator: inhaled β_2-agonist or ipratropium bromide as needed for symptoms, not to exceed 3-4 times daily.
STEP 3 Moderate Persistent	Daily medications • Inhaled corticosteroid, beclomethasone dipropionate MDI with spacer and face mask 400-800 µg daily or nebulized beclomethasone <= 1 mg twice daily. Consider short course of soluble prednisolone tablets, regular inhaled long-acting β_2-agonist or modified-release theophylline.	• Inhaled short-acting bronchodilator: inhaled β_2-agonist or ipratropium bromide as needed for symptoms, not to exceed 3-4 times daily.
STEP 2 Mild Persistent	• Either inhaled corticosteroid, beclomethasone dipropionate, 400-800 µg, or cromoglicate (use MDI with a spacer and face mask or use a nebulizer).	• Inhaled short-acting bronchodilator: inhaled β_2-agonist or ipratropium bromide as needed for symptoms, not to exceed 3-4 times daily.
STEP 1 Intermittent	• None needed.	• Inhaled short-acting bronchodilator: inhaled β_2-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 Childrens Over 5 Years Old

Preferred treatments are in bold print

	Long-term Preventive	**Quick Relief**
STEP 4 Severe Persistent	Daily medications • Inhaled corticosteroid, beclomethasone dipropionate 0.8-2 mg + • Long-acting bronchodilator: either long-acting inhaled β_2-agonist, and/or modified-release theophylline, and/or long-acting β_2 -agonist tablets or syrup + • corticosteroid tablets or syrup long term.	• Short-acting bronchodilator: inhaled β_2-agonist as needed for symptoms.
STEP 3 Moderate Persistent	Daily medications • Inhaled corticosteroid, beclomethasone diproprionate 0.8-2 mg daily in divided doses + if needed • Long-acting bronchodilator: either long-acting inhaled β_2-agonist, modified-release theophylline, or long-acting β_2-agonist tablets or syrup.	• Short-acting bronchodilator: inhaled β_2-agonist as needed for symptoms, not to exceed 3-4 times daily.
STEP 2 Mild Persistent	Daily medications • Either inhaled corticosteroid, beclomethasone dipropionate 100-400 µg twice daily, Sodium cromoglicate or modified-release theophylline.	• Short-acting bronchodilator: inhaled β_2-agonist as needed for symptoms, not to exceed 3-4 times daily.

STEP 1 Intermittent	• None needed.	• Short-acting bronchodilator: inhaled β_2-agonist as needed for symptoms (up to once daily) • Intensity of treatment will depend on severity of attack • Inhaled β_2-agonist or Sodium cromoglicate before exercise or exposure to allergen.
	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 β_2-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.

β_2-Adrenoceptor Agonists (β_2-Adrenoceptor Stimulants):

The adrenoreceptors in bronchi are mainly β_2 type and their stimulation causes bronchial muscles to relax. The β_2-adrenoceptor agonists include salbutamol, terbutaline, and fenoterol.

When salbutamol is given by inhalation (100-200 µg) the effect can last as long as 4 h 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.

Adverse Effects

Cardiovascular adverse effects (arrhythmias, palpitations and tachycardia) may occur with salbutamol, but are infrequent with inhaled preparations. Hypokalaemia may result from β_2-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 5) 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 h. It is used as an adjunct to β_2-agonist or corticosteroid therapy when additional bronchodilation is required but there is an increased risk of adverse effects with β_2-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 peparations 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.

Corticosteroids:

Inhaled Corticosteroids:

Inhaled corticosteroids, such as beclomethasone, 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 β_2-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 max. 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 may be used as ‘max. 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 β_2-agonists work more quickly. Ipratropium is also used as a bronchodilator in chronic obstructive pulmonary disease.

Aminophylline

Pregnancy Category-C

Indications	*Status asthmaticus, chronic obstructive pulmonary disease (COPD), reversible airway obstruction, chronic bronchitis, pulmonary edema, adjunct in treating CHF, apnoea in premature infants.*
Availability	**TABLETS** 100, 200, 225, and 350 mg; **INJECTION** 10 ml (250 mg/2 ml, 25 mg/ml); **ORAL LIQUID** 105 mg/5 ml; **SUPPOSITORY** 250 mg, 500 mg.
Dose	***Parenteral/Oral*** **Adult-** 250-500 mg orally or by slow i.v injection. Loading dose- 5 mg/kg. Maintainance dose- 0.5 mg/kg/h. **Child-** (6 months – 9 years) 1 mg/kg/h. (10 – 16 years) 800 µg/kg/h
Contraindications	Hypersensitivity to theophyllines.
Precautions	Alcohol dependence; hyperthyroidism; peptic ulcer; febrile illness; patients with severe heart, liver or kidney disease; lactation (Appendix 7b); renal impairment (Appendix 7d); interactions (Appendix 6c); congestive heart failure; neonates and elderly patients; epilepsy; high blood pressure; glaucoma; diabetes; allergies, pregnancy (Appendix 7c).
Adverse Effects	Convulsions; hypokalemia; dizziness, headache; palpitation, tachycardia, diarrhoea; anxiety; urinary retention; restlessness; tremors; abdominal pain; exfoliative dermatitis; erythema.

Storage Store protected from light and from atmospheric carbon dioxide. Injection: Store in single dose containers, from which carbon dioxide has been excluded. Do not allow contact with metals. Tablets: Store protected from light.

Beclomethasone*

Pregnancy Category-C

Schedule H

Indications *Chronic asthma not controlled by short-acting β_2-adrenoceptor agonists.*

Availability **INHALER** 100 and 200 µg per actuation; **CREAM** 5, 10, 15 (0.025%) and 20g (0.0125%); **OINTMENT** 20g.

Dose ***Aerosol inhalation***

Adult- Metered dose inhaler: 200 µg twice daily or 100 µg 3 to 4 times daily (in more severe cases, initially 600 to 800 µg daily).

High dose inhaler: 500 µg twice daily or 250 µg 4 times daily; if necessary may be increased to 500 µg 4 times daily.

Child- Metered dose inhaler: 50 to 100 µg 2 to 4 times daily or 100 to 200 µg twice daily.

High dose inhaler: not recommended.

Contraindication Acne; respiratory tract infection; pulmonary tuberculosis; ulcer; perioral dermatitis.

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; untreated fungal, bacterial and systemic viral infection, lactation (Appendix 7b); pregnancy (Appendix 7c).

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 β_2-adrenoceptor agonist or by transfer from aerosol to powder inhalation); rarely,; urticaria; rash; angioedema; telangiectasia; increased intraocular pressure; dermal thinning.

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.

Storage Store protected from moisture at a temperature not exceeding 30°C.

Budesonide

Preganacy Category-B

Schedule H

Indications *Nasal allergy, prophylaxis and treatment of seasonal and perennial allergic or vasomotor rhinitis, nasal polyposis, asthma.*

Availability **INHALER** 100 and 200 µg, **ROTACAP** 100, 200 and 400 µg, **NASAL SPRAY** 0.02% w/v.

Dose ***Asthma***

Adult- 200-400 µg Meter Dose Inhaler twice daily by inhalation, as dry powder inhaler 200-800 µg in single or two divided doses, as nebulised solution 0.5-1 mg twice daily.

Child- 50-400 µg Meter Dose Inhaler twice daily, as nebulised solution 0.25-0.5 mg twice daily.

Nasal polyps and allergic rhinitis: 200-400 µg/day by intranasal spray.

Contraindications Hypersensitivity; presence of infections or nasal ulcers.

Precautions Paradoxical bronchospasm; children, elderly, pregnancy (Appendix 7c), lactation; active or quiescent tuberculosis, interactions (Appendix 6c).

Adverse Effects Inhalation leads to hoarseness of voice, opportunistic fungal infection in oropharynx, respiratory infection, headache.

Epinephrine* (Refer Page No. 28 and 561)

Formoterol + Fluticasone propionate

Preganacy Category-B

Schedule H

Indications *Asthma, severe chronic obstructive pulmonary disease (COPD).*

Availability **Inhalation Aerosol-**

Formoterol	+	Fluticasone Propionate
6 µg	+	125 µg
6 µg	+	250 µg

Dose

Inhalation

Asthma: Adults- 1-2 inhalations twice daily.
Child- 1 rotacap twice daily.
(Rotacaps to be used with a rotahaler device only. Do not swallow the capsules).

COPD: Adults- 2 inhalations twice daily.
Not recommended for children below 4 years of age.

Contraindications

Hypersensitivity, acute asthma symptoms.

Precautions

Severe cardiovascular disorders, cardiac rhythm abnormalities, seizure disorder, diabetes, thyrotoxicosis, hypokalemia, pulmonary tuberculosis, pregnancy (Appendix 7c), lactation, interactions (Appendix 6c).

Adverse Effects

Headache, pharyngitis, throat irritation, upper respiratory tract infections, pneumonia, bronchitis, oral candidiasis, nausea, vomiting, diarrhea, chest pain, musculoskeletal pain, back pain, allergic reactions, wheezing, cough, skin rash, tremors, paradoxical bronchospasm, insomnia, adrenal suppression.

Storage

Store protected from light and moisture at a temperature not exceeding 30°C.

Hydrocortisone* (Refer Page No. 32, 355, 429 and 479)

Ipratropium*

Pregnancy Category-B

Schedule H

Indications

Chronic asthma; chronic obstructive pulmonary disease; bronchospasm; rhinorrhoea, rapid reversal of sinus rhythm.

Availability

METERED DOSE INHALER 200 doses (200 µg per actuation); **CAPSULE** 40 mg.

Dose

Aerosol inhalation

Adult- Metered dose inhaler; 20 to 40 µg, in early treatment up to 80 µg at a time, 3 to 4 times daily.

Child- Metered dose inhaler; up to 6 years; 20 µg 3 times daily. 6 to 12 years; 20 to 40 µg 3 times daily.

Contraindications

Glaucoma; hypersensitivity; bladder obstruction; urinary retention.

Precautions Prostatic hypertrophy; pregnancy (Appendix 7c); glaucoma (standard doses unlikely to be harmful; reported with nebulized drug; particularly in association with nebulized salbutamol); lactation; allergy to atropine or *Atropa belladona* leaves.

Adverse Effects Occasionally dry mouth; constipation; angina; tremors; palpitation; nasal congestion.

Storage Store protected from light and moisture.

Mometasone

Pregnancy Category-C

Schedule H

Indications *Dermatoses, prophylaxis and treatment of allergic rhinitis, nasal polyps, prophylaxis of asthma.*

Availability **CREAMS** 0.1% w/w; **LOTIONS** 0.1 % w/v; **OINTMENTS** 0.1% w/v; **NASAL SPRAY** 0.05% w/v.

Dose **Dermatoses: Adult** 0.1% cream or ointment or lotion.

Allergic rhinitis: 100 µg in each nostril once daily. Usual maintenance dose 50 µg in each nostril daily.

Asthma: Adult- 200-400 µg daily in 1-2 divided doses.

Child- 100 µg once daily.

Contraindications Hypersensitivity.

Precautions Hepatic and renal disease; myasthenia gravis, cardiovascular disease; ocular diseases; osteoporosis, glucocorticosteroid insufficiency; discontinue if irritation or sensitization occurs; interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Adrenal suppression; immunosuppression; anaphylaxis; musculoskeletal pain; depression; fatigue; sinusitis; oropharyngeal infections; upper respiratory tract infection; gastrointestinal disturbances; conjuctivitis; otitis media; local irritation and sensitization; bacterial skin infection; skin depigmentation; cataract; growth suppression.

Montelukast

Pregnancy Category-B

Schedule H

Indications *Prophylaxis of mild to moderate asthma.*

Availability **TABLETS** 5 and 10 mg.

Dose ***Oral***

Adult- 10 mg once a day.

Child- 2-5yrs: 4 mg once daily; 6-14 yrs: 5 mg once daily; ≥ 15 yrs: 10 mg once daily.

Contraindications Hypersensitivity.

Precautions History of liver disease, pregnancy (Appendix 7c).

Adverse Effects Headache; rashes; eosinophilia; neuropathy; Churg-strauss syndrome.

Storage Store protected from light and moisture.

Salbutamol*

Pregnancy Category-C

Schedule H

Indications *Prophylaxis and treatment of asthma; premature labour; reversible airway obstruction.*

Availability **TABLETS** 2 and 4 mg; **SYRUP** 2 mg/5 ml (100 ml); **CAPSULES** 4 mg; **INHALER** 100, 200 doses (100 µg per actuation).

Dose ***Oral***

Adult- Chronic asthma (when inhalation is ineffective): 2 to 4 mg, 3 or 4 times daily; in some patients up to max. of 8 mg, 3 or 4 times daily.

Child- Chronic asthma (when inhalation is ineffective): under 2 years; 100 µg/kg, 4 times daily. 2 to 6 years; 1 to 2 mg, 3 to 4 times daily.

Slow intravenous injection

Adult- Severe acute bronchospasm: 250 µg, repeated if necessary.

Aerosol inhalation and intramuscular or subcutaneous injection

Adult- Relief of acute bronchospasm: 100 to 200 µg (1 to 2 puffs) by aerosol inhalation and 500 µg by intramuscular or subcutaneous injection; repeated every 4 h if necessary.

Child- Relief of acute bronchospasm: 100 µg (1 puff) increased to 200 µg (2 puffs); if necessary.

Aerosol inhalation

Adult- Prophylaxis of exercise-induced bronchospasm: 200 µg (2 puffs).

Chronic asthma (as adjunct in stepped treatment): 100 to 200 µg (1 to 2 puffs), up to 3 to 4 times daily.

Child- Prophylaxis of exercise-induced bronchospasm: 100 µg (1 puff) increased to 200 µg (2 puffs); if required.

Chronic asthma (as adjunct in stepped treatment): 100 µg (1 puff) 3 to 4 times daily, increased to 200 µg (2 puffs) 3 to 4 times daily; if necessary.

Inhalation of nebulized solution

Adult- Severe acute asthma or chronic bronchospasm unresponsive to conventional treatment: 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- Severe acute asthma or chronic bronchospasm unresponsive to conventional treatment, 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. Under 18 months: clinical efficacy uncertain (transient hypoxaemia may occur- consider oxygen supplementation).

Contraindications

$\beta_2$agonists are contraindicated in cardiac disease; antepartum haemorrhage; intrauterine infection; intrauterine fetal death; placenta praevia; abruptio placenta; threatened miscarriage; cord compression; eclampsia or severe pre-eclampsia; diabetes mellitus; thyrotoxicosis.

Precautions Hyperthyroidism; myocardial insufficiency; arrhythmias; susceptibility to QT-interval prolongation; hypertension; pregnancy (Appendix 7c) (but appropriate to use; see also notes above); lactation (Appendix 7b); diabetes mellitus-especially intravenous administration (monitor blood glucose; ketoacidosis reported); interactions (Appendix 6c).

Adverse Effects Hypokalaemia after high doses; 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.

Storage Store protected from light and moisture at a temperature not exceeding 30°C.

Terbutaline* (Refer Page No. 502)

Theophylline

Pregnancy Category-C

Indications *Chronic asthma including nocturnal asthma; acute severe asthma; apnoea of prematurity.*

Availability **TABLETS** 100, 150, 200, 250, 300, 400 and 600 mg; **CAPSULES** 125, 200, 250 and 400 mg; **SYRUP** 5 mg/5 ml (100 ml) Aminophylline, 100 ml (50 mg/5ml), 200 ml (80 mg/5ml), (125 mg/5ml); **INJECTION** 10 ml ampoule (25 mg/ml).

(Theophylline tablets available in combination with aminophylline).

Dose ***Oral***

Adult- Chronic asthma (as tablets): 100 to 200 mg, 3 to 4 times daily after food.

Chronic asthma (as modified-release tablets): 300 to 450 mg every 12 h.

Nocturnal asthma (as modified-release tablets): total daily requirement as single evening dose.

Child- Chronic asthma (as tablets); over 12 years: 100 to 200 mg, 3 to 4 times daily after food.

Slow intravenous injection and infusion

Adult- Acute severe asthma; by slow intravenous injection (over at least 20 min): 5 mg/kg. Maintenance by intravenous infusion: 500 µg/kg/hr.

Child- Acute severe asthma; by slow intravenous injection (over at least 20 min): 5 mg/kg. Maintenance by intravenous infusion; 6 months to 9 years: 1 mg/kg/h. 10 to 16 years: 800 µg/kg/h, adjusted according to plasma concentration.

Note: Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage and vice versa.

Contraindications Porphyria; known hypersensitivity to ethylenediamine (for aminophylline).

Precautions Cardiac disease; hypertension; hyperthyroidism; peptic ulcer; epilepsy; hepatic impairment; pregnancy (Appendix 7c); lactation (Appendix 7b); elderly; fever; smokers may require larger or more frequent doses; interactions (6b, 6c).

Adverse Effects Nausea vomiting and other gastrointestinal disturbances; restlessness; anxiety; tremor; palpitations; headache; insomnia; dizziness; convulsions; arrhythmias and hypotension-especially if given by rapid injection; urticaria; erythema and exfoliative dermatitis-resulting from hypersensitivity to ethylenediamine component of aminophylline; neurotoxicity; hypokalemia; metabolic acidosis; gastrointestinal haemorrhage.

Storage Store protected from moisture.

23.2 Antitussives (Cough suppressants)

Cough acts as protective reflux. It is helpful in the expulsion of respiratory secretion and other foreign particles from respiratory tract. Cough is of non- productive and productive type. Non-productive cough should be suppressed, whereas productive cough should not be suppressed. Cough suppressants are used only for the control of non-productive cough.

Codeine* (Refer Page No. 10 and 72)

Dextromethorphan*

Pregnancy Category-C

Indications	*Dry cough.*
Availability	**TABLET** 10 mg; **SYRUP** 15 mg/5 ml and 30 mg/5 ml.
Dose	***Oral***
	Adult- 10 – 20 mg every 4 hour or 30 mg every 6 – 8 hours.
	Child- 6 – 12 years: 5 – 10 mg every 4 hours or 15 mg every 6 – 8 hours.
	2 – 6 years: 2.5 – 5 mg every 4 hours or 7.5 mg every 6 – 8 hours.
Contraindications	Patients at risk of developing respiratory failure; persistent or chronic cough; patients receiving monoamine oxidase inhibitors (with or within 2 weeks).
Precautions	Moderate/severe renal impairment; liver disease, atopic children; patients confined to supine position; debilitated patients; third trimester of pregnancy (Appendix 7c); asthma; interactions (Appendix 6a, 6c).
Adverse effects	Dependency; dizziness; restlessness; mental confusion; excitation; gastrointestinal disturbance.

24. Hormones, Contraceptives and Related Drugs 459

24. Hormones, Contraceptives and Related Drugs

24.1 Contraceptives

24.1.1 Oral 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 dysmenorrhoea. 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 h 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 occuring 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 160 mmHg systolic and 100 mmHg diastolic;
- 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; lactation 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 72 h of unprotected intercourse; alternatively, levonorgestrel 750 µg can be taken within 72 h of unprotected intercourse followed 12 h later by another 750 µg. 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 h 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.

Centchroman
(Non-steroidal oral contraceptive)

Pregnancy Category-X

Schedule H

Indications *Contraception.*

Availability **TABLET** 30 mg.

Dose ***Oral***

30 mg tablets. A single tablet should be taken twice a week (on a sunday and a wednesday) for the first three months and then weekly (every sunday) thereafter.

Contraindications Medical history of liver disease, jaundice; ovarian disease (polycystic ovaries); cervical hyperplasia; cervicitis; chronic renal disorders.

Precautions Prolongation of menstrual cycles may be experienced by some individuals. Delayed menstruation is inconsequential if dosages have not been missed. In case of delay exceeding 15 days, pregnancy should be ruled out with routine investigations. Administration should be discontinued immediately if pregnancy is confirmed (Appendix 7c).

Adverse Effects Water retention; tender breasts; acne; heavy menstruation.

'Ethinylestradiol + Levonorgestrel'* and 'Ethinylestradiol + Norethisterone'*

Pregnancy Category-X

Schedule H

Indications *Contraception; menstrual symptoms; endometriosis.*

Availability **TABLETS**
Levonorgestrel + Ethinylestradiol
0.15 mg + 0.03 mg
0.25 mg + 0.05 mg
Levonorgestrel 0.15 mg + Ethinylestradiol 0.03 mg + Ferrous fumarate 60 mg.
Norethisterone + Ethinylestradiol
0.5 mg + 0.03 mg
1.0 mg + 0.03 mg

Dose ***Oral***

Adult- Contraception: 1 tablet (pill) daily for 21 days; subsequent courses repeated after 7-day pill-free interval (during which withdrawal bleeding occurs).

Each tablet (pill) should be taken at approximately the same time each day; if delayed by longer than 24 h contraceptive protection may be lost. It is important to bear in mind that the critical time for loss of protection is when a pill is omitted at the beginning or end of a cycle (which lengthens the pill-free interval).

Note: Ethinylestradiol with levonorgestrel and ethinylestradiol with norethisterone are representative combined oral contraceptive preparations. Various combinations can serve as alternatives.

Contraindications

Use within 3 weeks of birth; lactation until weaning or for first 6 months after birth (Appendix 7b); personal history of 2 or more risk factors for venous or arterial thrombosis (see notes above); heart disease associated with pulmonary hypertension or risk of embolism; migraine (see below); history of sub-acute bacterial endocarditis; ischaemic cerebrovascular disease; liver disease (Appendix 7a), including disorders of hepatic secretion such as Dubin-Johnson or Rotor syndromes, infectious hepatitis (until liver function normal); porphyria; systemic lupus erythematosus; liver adenoma; history of cholestasis with oral contraceptives; gallstones; estrogen-dependent neoplasms; neoplasms of breast or genital tract; undiagnosed vaginal bleeding; history of pruritus during pregnancy, chorea, herpes, deteriorating otosclerosis, cholestatic jaundice; diabetes mellitus (if either retinopathy, neuropathy or if more than 20 years duration); after evacuation of hydatidiform mole (until return to normal of urine and plasma gonadotrophin values).

Migraine with typical focal aura; migraine without aura regularly lasting over 72 h duration despite treatment; migraine treated with ergot derivatives; migraine without focal aura or controlled with 5-HT_1 agonist.

Precautions

Risk factors for venous thromboembolism and arterial disease (see notes above); migraine (see below); hyperprolactinaemia (seek specialist advice); some types of hyperlipidaemia; gallbladder disease; severe depression; long-term immobilization (see also Travel below); sickle-cell disease; inflammatory bowel disease including Crohn'sdisease, interactions (Appendix 6c, 6d).

Patients should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than one hour).

Women taking oral contraceptives may be at increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 h). The risk may be reduced by appropriate exercise during the journey and possibly by wearing elastic hosiery; pregnancy (Appendix 7c).

Adverse Effects Nausea, vomiting, headache; breast tenderness; increase in body weight; thrombosis; changes in *libido;* depression; chorea; skin reactions; chloasma; hypertension; impairment of liver function; 'spotting' in early cycles; absence of withdrawal bleeding; breast cancer (small increase in risk of breast cancer during use which reduces during the 10 years after stopping; risk factor seems related to age at which contraceptive is stopped rather than total duration of use; small increase in risk of breast cancer should be weighed against the protective effect against cancers of the ovary and endometrium which persists after stopping); dizziness, stomach upset, bloating, mental and mood changes.

Levonorgestrel

Pregnancy Category-X

Schedule H

Indications *Emergency hormonal contraception.*

Availability **TABLETS** 0.75 and 1.5 mg.

Dose ***Oral***

Adult- Contraception: 1 tablet ('pill') (30 µg) daily, starting on the first day of the cycle and then continuously.

Contraindications Progestogen-only oral contraceptives; undiagnosed vaginal bleeding; severe arterial disease; liver tumours; breast cancer; thromboembolic disorders; sickle-cell anaemia; porphyria; after evacuation of hydatidiform mole (until return to normal urine and plasma gonadotrophin values); progestogen-only emergency hormonal contraceptives; severe liver disease.

Precautions Possible small increase in risk of breast cancer; cardiac disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndrome; ovarian cysts; active liver disease, recurrent cholestatic jaundice, history of jaundice in pregnancy (Appendix 7c); increase in frequency or severity of headache (discontinue pending investigation); lactation (Appendix 7b); pregnancy (Appendix 7c).

Adverse Effects Menstrual irregularities (including oligomenorrhoea and menorrhagia); nausea, vomiting, headache, dizziness; breast discomfort, depression; skin disorders; disturbances of appetite; weight increase; change in *libido*.

24.1.2 Injectable Hormonal Contraceptives

Medroxyprogesterone

Pregnancy Category-X

Schedule H

Indications *Parenteral progestogen-only contraception (short- term or long-term); menstrual symptoms and endometriosis; dysmenorrhoea.*

Availability **TABLETS** 2.5, 5 and 10 mg; **INJECTION** 150 mg (1 ml VIAL/PREFILLED SYRINGE).

Dose ***Deep intramuscular injection***

Adult- Contraception (short-term): 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if lactating). Contraception (long-term); as for short-term, repeated every 3 months.

Mild to moderate endometriosis: 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle. Dysfunctional uterine bleeding; 2.5 to 10 mg daily for 5 to 10 days beginning on day 16 to 21 of cycle for 2 cycles. Secondary amenorrhoea; 5 to 10 mg daily for 5 to 10 days beginning on day 16 to 21 of cycle for 3 cycles.

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.

Contraindications Pregnancy (Appendix 7c); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 7a); severe arterial disease; porphyria; active thromophlebitis; lactation (Appendix 7b).

Precautions Small increase in possible risk of breast cancer; migraine; liver disease; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease; fluid retention, CNS disorder and convulsions.

Adverse Effects Menstrual irregularities; delayed return to fertility; reduction in bone mineral density; weight gain; depression; rarely, anaphylaxis; abdominal pain, asthenia, breast pain, bloating, insomnia, vaginitis.

Storage Store protected from light and moisture.

Norethisterone* (Refer Page No. 496)

Pregnancy Category-X

Schedule H

Indications *Parenteral progestogen-only contraception (short-term).*

Availability **TABLETS** 1 and 5 mg **INJECTION** 1 ml ampoule (200 mg/ml).

Dose ***Deep intramuscular injection*** (into the gluteal muscle).

Adult- Short-term contraception: 200 mg within 5 days of cycle or immediately after parturition; repeated after 2 months.

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.

Contraindications Pregnancy (Appendix 7c); breast or endometrial cancer; severe liver disease (Dubin-Johnson or Rotor's syndromes) (Appendix 7a); history of jaundice, pruritus, herpes or of deteriorating otosclerosis during pregnancy; 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; epilepsy, hepatitis, amenorrhoea, herpes gestation.

Precautions Possible small increase in risk of breast cancer; migraine; liver dysfunction; depression; diabetes mellitus; previous ectopic pregnancy; cardiac and renal disease; interactions (Appendix 6b); vaginal bleeding; blood clots; seizures, lactation (Appendix 7b).

Adverse Effects Bloating; breast discomfort; headache; dizziness, depression; nausea; menstrual irregularities; rarely; weight gain; hepatitis; cataract; optic neuritis; mental discomfort.

Storage	Tablets: Store protected from light and moisture. Injection: Store protected from light.

24.1.3 Intrauterine 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 role 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.

Hormone Releasing IUD*

Indications	*For contraception.*
Availability	At Family Welfare clinics or speciality centres.
Dose	For contraception, the device can be inserted at any time between day 4 and day 12 after the start of menstrual bleeding; not to be fitted during heavy menstrual bleeding. Emergency contraception, the device may be inserted up to 120 h (5 days) after unprotected intercourse, at any time of menstrual cycle; if intercourse has occurred more than 5 days previously, device can still be inserted up to 5 days after the earliest likely calculated day of ovulation; device can be removed at the beginning of menstruation if no longer required.
Contraindications	Abnormal pap smear or abnormal vaginal bleeding.
Adverse Effects	Heavy bleeding, perforation of uterus; cramps.

IUD Containing Copper*

Indications	*Contraception; emergency contraception.*
Availability	Single IUD in pouch pack.
Dose	For contraception, the device can be inserted at any time between day 4 and day 12 after the start of menstrual bleeding; not to be fitted during heavy menstrual bleeding. Emergency contraception, the device may be inserted up to 120 h (5 days) after unprotected intercourse, at any time of menstrual cycle; if intercourse has occurred more than 5 days previously, device can still be inserted up to 5 days after the earliest likely calculated day of ovulation; device can be removed at the beginning of menstruation if no longer required.

Contraindications	Pregnancy; 48h-4 weeks post partum; puerperal sepsis; postseptic abortion; cervical or endometrial cancer; pelvic inflammatory disease; recent sexually transmitted disease (if not fully investigated and treated); pelvic tuberculosis; unexplained uterine bleeding; malignant gestational trophoblastic disease; distorted or small uterine cavity; copper allergy; Wilson's disease; medical diathermy; abnormal pap smear or abnormal vaginal bleeding.
Precautions	Anaemia; heavy menstrual bleeding, endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, history of ectopic pregnancy or tubal surgery, fertility problems, nulliparity and young age, severely scarred uterus or severe cervical stenosis, valvular heart disease (requires antibacterial cover)-avoid if prosthetic valve or history of endocarditis; HIV infection or immunosuppressive therapy (risk of infection-avoid if marked immunosuppression); joint and other prostheses; increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion and 4-6 weeks afterwards-counsel women to see doctor promptly if significant symptoms such as pain; anticoagulant therapy; remove if pregnancy occurs (consider possibility of ectopic pregnancy).
Adverse Effects	Uterine or cervical perforation, displacement, expulsion; pelvic infection exacerbated; heavy menstrual bleeding; dysmenorrhoea; pain and bleeding and occasionally epileptic seizure or vasovagal attack on insertion.

24.1.4 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.

Hormone Therapy (HT):

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. HT should not be prescribed with the aim of reducing the incidence of heart disease. HT 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; Medroxyprogesterone acetate (see also chapter 21.4.2) may be given in a dose of 10 mg daily for the last 12-14 days of each estrogen HT cycle. Alternatively, norethisterone 1 mg daily may be given on the last 12-14 days of each 28-day estrogen cycle.

HT 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, HT can be given until the approximate age of natural menopause (until age 50 years).

For longer-term use of HT 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 HT 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 HT; 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 HT. 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 HT increases the risk of breast cancer slightly. The increased risk is related to the duration of HT use and this excess risk disappears within about 5 years of stopping. The risk of breast cancer is greater with combined HT (an estrogen

and a progestogen) than with estrogen-only HT (but estrogen alone may not be suitable for women with intact uterus).

Epidemiological studies indicate that in women aged between 50 and 65 years not using HT, about 32 cases of breast cancer will be diagnosed in every 1000 women. In those using HT, the risk of breast cancer is increased as follows:

- Women using *combined HT* with an estrogen and a progestogen for 5 years, about 6 additional cases in 1000; in those using combined HT for 10 years, about 19 additional cases in 1000
- Women using *estrogen-only HT* for 5 years, about 2 additional cases in 1000; in those using estrogen-only HT for 10 years, about 5 additional cases in 1000.

HT does not provide contraception. If a potentially fertile woman needs to use HT, non-hormonal contraceptive measures are necessary.

Precautions for patients on HT undergoing surgery and reasons to stop HT are the same as those for hormonal contraceptives.

Ethinylestradiol*

Pregnancy Category-X

Schedule H

Indications — *Hormone replacement for menopausal symptoms; osteoporosis prophylaxis; palliation in breast cancer in men and postmenopausal women; contraception in combination with a progestogen; dysfunctional uterine bleeding, prostatic carcinoma.*

Availability — **TABLETS** 0.01, 0.05 and 1 mg; **INJECTION** 1 ml ampoule (10 mg/ml).

Dose — ***Oral***

Adult- Hormone replacement: 10 to 20 µg daily. Palliation in breast cancer in postmenopausal women: 0.1 to 1 mg 3 times daily.

Contraindications — Pregnancy (Appendix 7c); estrogen-dependent cancer; active thrombophlebitis or thromboembolic disorders or history of recent venous thromboembolism (unless already on anticoagulant therapy); undiagnosed vaginal bleeding; lactation (Appendix 7b); liver disease (where liver function tests have failed to return to normal), Dubin-Johnson and Rotor syndromes (or monitor closely); jaundice; cerebrovascular disease; hepatic carcinoma; CV disease; estrogen dependent cancer.

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 6c, 6d); hepatic impairment (Appendix 7a).

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; impotence; hypertension.

Storage Store protected from light.

Tamoxifen*

Pregnancy Category-D

Schedule G

Indications *Adjuvant treatment for estrogen receptor positive breast cancer, metastatic breast cancer, male infertility, anovulatory infertility.*

Availability **TABLETS** 10, 20, 25, 40 and 100 mg.

Dose

Breast cancer:
Adult- 20 mg daily as a single dose or in 2 divided doses. max. 40 mg/day.

Anovulatory infertility:
Adult- 20 mg daily on second- fifth day of the menstrual cycle. max.- 80 mg/day.

Contraindications Hypersensitivity, deep vein thrombosis, pulmonary embolism, pregnancy (Appendix 7c) (exclude before treatment and advise non-hormonal contraception if appropriate), lactation (Appendix 7b).

Precautions If patient experiences swelling around ankles or legs, decrease salt intake, cystic ovarian swellings in premenopausal woman.

Adverse Effects

Hypersensitivity reactions such as angioedema, Steven's Johnson syndrome and bullous pemphigoid. Hot flushes, nausea, vomiting; vaginal discharge and bleeding, menstrual irregularities, increased risk of venous thromboembolism; distaste of food; depression; hair thinning; hypercalcaemia; peripheral oedema; decreased platelet count; increased pain and hypercalcaemia with bony maetastasis; tumor flare; liver enzyme changes (rarely, cholestasis); hepatitis; hepatic necrosis; hypertriglyceridaemia (sometimes with pancreatitis).

Storage

Store protected from light and moisture.

24.2 Hormones

24.2.1 Adrenal Hormones and synthetic Substitutes

Corticosteroids 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 (adrenocorticotrophic 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 undergo 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 gluco-

corticoid 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.

Adverse Effects 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 h after moderate surgery or for 48-72 h 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 on exposure. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation;

rash is not necessarily a prominent feature.

Passive immunization with varicella-zoster immunoglobulin 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 may be needed.

Dosage and Administration:

Adverse effects of systemic glucocorticoids, including suppression of the Hypothalamo-Pituitary-Adrenal (HPA) 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 beclomethasone may be used (chapter 20.1). 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, dura-

tion 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* (Refer Page No. 30)

Pregnancy Category-C

Schedule H

Indications	*Suppression of inflammatory and allergic disorders; shock; diagnosis of Cushing syndrome; congenital adrenal hyperplasia; cerebral oedema; respiratory distress syndrome.*
Availability	**TABLETS** 0.5, 2 and 4 mg; **INJECTION** 2 ml vial (4 mg/ml). **CREAM** 5 and 15 gm (0.1% w/w).
Dose	***Oral***
	Adult- 0.5 to 10 mg daily.
	Intramuscular injection or slow intravenous injection or intravenous infusion
	Adult- Initially 0.5 to 20 mg daily.
	Child- 200 to 500 µg/kg daily.

Adult- Cerebral oedema: 10 mg initially by intravenous injection, then 4 mg by intramuscular injection every 6 h, as required for 2-10 days.

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); diabetes, hypertension, psychosis, osteoporosis, gastric ulceration.

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, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy; lactation (Appendix 7b); interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Refer adverse effects of corticosteroids.

Hydrocortisone* (Refer Page No. 32, 355 and 429)

Pregnancy Category-C

Schedule H

Indications *Adrenocortical insufficiency; hypersensitivity reactions including anaphylactic shock; inflammatory bowel disease; asthma; perineal trauma; joint inflammation; seborrheic dermatitis.*

Availability **TABLETS** 5, 10 and 20 mg, **CREAM** 10g (1% w/w), **OINTMENT** 1%, 2.5% w/w **INJECTION** 100, 200 and 400 mg vial (25 mg/5 ml).

Dose ***Oral***

Adult-20 to 30 mg daily in divided doses (usually 20 mg in the morning and 10 mg in early evening).

Child-400-800 µg/kg/day in 2-3 divided doses.

Slow intravenous injection or intravenous infusion

Adult- Acute adrenocortical insufficiency: 100 to 500 mg, 3 to 4 times in 24 h or as required.

Child- Up to 1 year: 25 mg; 1 to 5 years: 50 mg; 6 to 12 years: 100 mg.

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); ulcers.

Precautions Refer corticosteroids; lactation (Appendix 7b); interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c).

Adverse Effects Refer adverse effects of corticosteroids.

Methyl Prednisolone*

Pregnancy Category-C

Schedule H

Indications *Corticosteroid responsive conditions such as severe allergic rhinitis, asthma, rheumatoid arthritis, osteoarthritis, collagen disease, dermatoses.*

Availability **TABLETS** 4, 8, 16 and 24 mg; **INJECTION** vials 40, 125, 500 and 1000 mg, 2 ml ampoule (80 mg/2 ml)**.**

Dose ***Oral***

Adult- Asthma, allergies and dermatological conditions: 40 and 120 mg.

Dose should be regulated in accordance with severity of condition; large joints- 20 to 80 mg; medium joints- 10 to 40 mg; small joints- 4 to 10 mg directly in bursae.

Contraindications Systemic fungal infection (unless specific antimicrobial therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished); hypersensitivity.

Precautions Refer notes above; interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).

Adverse Effects Refer adverse effects of corticosteroids.

Storage Store protected from light at a temperature not exceeding 30°C. The injection should not be allowed to freeze.

Prednisolone* (Refer Page No. 35, 436 and 557)

Pregnancy Category-C

Schedule H

Indications

Suppression of inflammatory and allergic reactions; with antineoplastic drugs for acute leukaemias and lymphomas; asthma; rheumatic disorder; hematologic disorder.

Availability

TABLETS 5, 10, 20 and 40 mg; **INJECTION** 1 ml vial (40 mg/ml); **SYRUP** 60 ml (5 mg/5 ml and 15 mg/5 ml).

Dose

Oral

Adult- Suppression of inflammatory and allergic disorders: initially up to 10 to 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. Maintenance dose 2.5 to 15 mg daily or higher; cushingoid features are increasingly likely with doses above 7.5 mg daily.

Myasthenia gravis: initially 10 mg on alternate days, increased in steps of 10 mg on alternate days to 1-1.5 mg/kg (max. 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).

Child- Fractions of adult dose may be used (At 1 year: 25% of adult dose; at 7 years: 50%; and at 12 years: 75%) but clinical factors must be given due weight.

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

Refer notes above; hepatic impairment (Appendix 7a); lactation (Appendix 7b); interactions (Appendix 6c, 6d); pregnancy (Appendix 7c).

Adverse Effects

Refer Adverse effects of Corticosteroids.

24.2.2 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.

Danazol*

Pregnancy Category-X

Schedule H

Indications	*Endometriosis, fibrocystic mastitis, hereditary angioedema, menorrhagia, gynaecomastia, precocious puberty.*
Availability	**TABLETS/CAPSULES** 50, 100 and 200 mg.
Dose	Endometriosis: **Adult-** 200 to 600 mg daily in 2 divided doses. Fibrocystic mastitis: **Adult-** 100 to 400 mg daily in 2 divided doses. Hereditary angioedema: **Adult-** 200 mg twice or thrice daily. Gynaecomastia: **Adult-** Initially 400 mg daily in 4 divided doses for 6 months. **Child-** Initially 200 mg daily, may increase to 400 mg after 2 months.

Menorrhagia: **Adult-** 200 mg once daily.

Contraindications Hepatic dysfunction; undiagnosed vaginal bleeding; porphyria; thromboembolic complication; hypersensitivity; pregnancy (Appendix 7c), lactation.

Precautions Use with caution in patients with migraine, headache, heart, liver or kidney disease. History of seizures; abnormal bleeding; previous strokes; severe hypertension; diabetes mellitus, polycythaemia; interactions (Appendix 6c).

Adverse effects Androgen like effects including weight gain, acne, deepening of voice; seborrhoea; edema; hair loss; amenorrhoea; hirsutism; benign intracranial hypertension; dizziness.

Storage Store protected from light.

Testosterone*

Pregnancy Category-X

Schedule H

Indications *Hypogonadism; palliative treatment of advanced breast cancer in women.*

Availability **INJECTION** 10 ml ampoule (25 mg/ml, 50 mg/ml, 100 mg/ml).

Dose ***Slow intramuscular injection***

Adult- Hypogonadism: initially 200 to 250 mg every 2 to 3 weeks; maintenance dose 200 to 250 mg every 3 to 6 weeks. Breast cancer: 250 mg, every 2 to 3 weeks.

Contraindications Breast cancer in men; prostate cancer; hypercalcaemia; pregnancy (Appendix 7c), lactation (Appendix 7b); nephrosis; history of primary liver tumours.

Precautions Cardiac, renal or hepatic impairment (Appendix 7a), elderly; ischaemic heart disease; hypertension, epilepsy; migraine; diabetes mellitus; skeletal metastases (risk of hypercalcaemia); regular examination of prostate during treatment; prepubertal boys; breathing disturbance.

Adverse Effects Prostate abnormalities and prostate cancer; headache, depression, gastrointestinal bleeding, nausea; polycythaemia; cholestatic jaundice; changes in *libido;* gynaecomastia, anxiety, asthenia; generalized paraesthesia; electrolyte disturbances including sodium retention with oedema and hypercalcaemia; increased bone growth; androgenic effects such as hirsutism, male-pattern baldness, seborrhoea, acne, priapism, precocious sexual development and premature closure of epiphyses in pre-pubertal males, virilism in females, and suppression of spermatogenesis in men.

Storage Store protected from light.

24.2.3 Drugs for Erectile dysfunction

Sildenafil

Schedule H

Indications *Erectile dysfunction.*

Availability **TABLETS** 25, 50 and 100 mg.

Dose 50 mg about 1 hour before sexual intercourse, maximum 100 mg per dose and not more than once in 24 hours.

Elderly (greater than 65 yrs)- lower initial dose at 25 mg.

Contraindications Hypersensitivity; coronary heart disease; patients on nitrates.

Precautions Liver or kidney disease; peptic ulcer; bleeding disorder; leukemia, sickle cell anaemia, myloma predisposing priapism; recent history of stroke, myocardial infarction, arrthymias, unstable angina; anatomical deformation of penis; interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Headache, nasal congestion, dizziness, flushing; fall in blood pressure; diarrhoea; impairment of colour vision; AV-block, angina pectoris, cardiac arrest, myocardial infarction, cerebral thrombosis, abnormal LFT, hypoglycaemia; retinal vascular disease; photosensitivity, paresthesia; tremor; depression.

24.3 Insulin and Other Anti-Diabetic Agents

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 β-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 pregnancy (second and third trimesters) may increase insulin requirements; renal or hepatic impairment and some endocrine disorders (for example Addison's disease, hypopituitarism) or coelic 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 9 mmol/litre (4-7 mmol/L before meals, <9 mmol/L) 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 hour; 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 min 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 hour 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. Diabetic 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 h. 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 min 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:

- 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 min), a peak action between 2 and 4 h, and a duration of action up to 8 h. Soluble insulin by the intravenous route is reserved for urgent treatment and fine control in serious illness and perioperative state. When injected

intravenously, soluble insulin has a very short half-life of only about 5 min.

When injected subcutaneously, intermediate-acting insulins have an onset of action of approximately 1-2 h, a maximal effect at 4-12 h and a duration of action of 16-24 h. 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.

Oral Antidiabetic Drugs

Oral antidiabetic (hypoglycaemic) drugs are used for non-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 h 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 lactation 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 over-

weight 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 3g 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 problem) 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*

Pregnancy Category-C

Schedule G

Indications	*Type II diabetes mellitus.*
Availability	**TABLETS** 1.25, 2.5 and 5 mg.
Dose	***Oral*** **Adult-** initially 5 mg once daily with or immediately after breakfast; max. 15 mg daily. **Elderly-** 2.5 mg, but it should preferably be avoided, adjusted according to response (max. 15 mg daily).
Contraindications	Ketoacidosis; porphyria; lactation (Appendix 7b).
Precautions	Renal impairment; hepatic impairment (Appendix 7a); elderly; substitute insulin during severe infection, trauma, surgery (see notes above); interactions (Appendix 6b, 6c); diabetic coma; pregnancy (Appendix 7c).
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; cholestatic jaundice.

Gliclazide

Pregnancy Category-C

Schedule H

Indications *Type II diabetes mellitus.*

Availability **TABLETS** 20, 30, 40, 80 and 160 mg; **MODIFIED RELEASE TABLETS** 30 and 60 mg; **CAPSULES** 30, 40, 60 and 80 mg.

Dose 40- 320 mg daily, doses >160 mg daily may be given in 2 divided doses.

Modified release tablets 30-120 mg daily.

Contraindications Type I diabetes mellitus, severe renal and hepatic impairment, diabetic ketoacidosis, pregnancy (Appendix 7c), lactation.

Precautions Monitor blood glucose concentration, increased risk of hypoglycaemia in elderly; debilitated patients; renal and hepatic impairment, metabolic stressful situations; interactions (Appendix 6c).

Adverse Effects Cutaneous reactions; blood dyscrasias, gastrointestinal disturbances; cholestatic jaundice.

Glimepiride

Pregnancy Category-C

Schedule H

Indications *Type II diabetes mellitus.*

Availability **TABLETS** 1, 2, 3 and 4 mg.

Dose **Adult** 1-2 mg daily.

Max dose 8 mg daily.

Contraindications Hypersensitivity; pregnancy (Appendix 7c); diabetic ketoacidosis.

Precautions Elderly; hepatic and renal impairment; interactions (Appendix 6b, 6c); monitor blood-glucose concentration; lactation.

Adverse Effects Hypoglycaemia; weight gain.

Storage Store protected from moisture at temperature not exceeding 30°C.

Glipizide

Pregnancy Category-C

Indications *Type II diabetes mellitus.*

Availability **TABLETS** 2.5, 5, 7.5 and 10 mg.

Dose 2.5-20 mg once or twice daily. Maximum 40 mg daily.

Contraindications Hypersensitivity; type I diabetes mellitus, ketoacidosis with or without coma; severe hepatic or renal insufficiency; pregnancy (Appendix 7c), lactation.

Precautions Stress; fever; trauma; infection or surgery; elderly; thyroid impairment; monitor blood glucose concentration.

Adverse Effects Hypoglycemia, nausea, diarrhoea, allergic skin reactions, thrombocytopenia, leucopenia, agranulocytosis, jaundice, hemolytic anaemia.

Storage Store protected from moisture.

Glucagon*

Pregnancy Category-B

Schedule H

Indications *Severe hypoglycaemia and radiological examination of gastrointestinal tract.*

Availability **INJECTION** (powder for reconstitution)- 1 mg vial with pre-filled syringe containing water for injection.

Dose ***Parenteral***

Severe hypoglycaemia:
Adult and child over 8 years (or body weight over 25 kg)- 1 mg by s.c, i.m or i.v route.

Child under 8 years (or body weight under 25 kg)- 500 µg, if no response within 10 minutes i.v glucose must be given.

As diagnostic aid in gastrointestinal examination: Adult- 1-2 mg by i.m or 0.2-2 mg by i.v. injection.

Diagnosis of pheochromocytoma: 1 mg i.v.

Contraindications Pheochromocytoma; hypersensitivity.

Precautions Patients with insulinoma, glucagonoma, monitor prothrombin time, starvation and adrenal insufficiency, ineffective in chronic hypoglycaemia, alcohol-induced hypoglycaemia, pregnancy (Appendix 7c), lactation, interactions (Appendix 6b, 6c).

Adverse effects Hypokalemia; nausea, vomiting, abdominal pain; rarely, hypersensitivity.

Insulin*

Pregnancy Category-B

Schedule H, G

Indications	*Diabetes mellitus; diabetic emergencies and at surgery; diabetic ketoacidosis or coma.*
Availability	**INJECTION** (multi-dose vials/prefilled syringes/cartridges) - 40 and 100 IU/ml.
Dose	***Subcutaneous, intramuscular, intravenous injection or intravenous infusion.*** **Adult and Child-** Diabetes mellitus: according to individuals requirement.
Precautions	See notes above; reduce dose in renal impairment, lactations; interactions (Appendix 6a, 6b, 6c); pregnancy (Appendix 7c).
Adverse Effects	Hypoglycaemia in overdose; localized, and rarely, generalized allergic reactions; lipodystrophy at injection site.
Storage	Store in multi dose container in a refrigerator (2 to 8^{o}C). It should not be allowed to freeze.

Intermediate Acting Insulin*

Insulin Zinc

Schedule G

Indications	*Diabetes mellitus.*
Availability	**INJECTION** 40 and 80 IU/ml.
Dose	***Subcutaneous injection*** **Adult and Child-** Diabetes mellitus: according to individuals requirement.
Precautions	See notes above; reduce dose in renal impairment; lactation.
Adverse Effects	Hypoglycaemia in overdose; localized, and rarely, generalized allergic reactions; lipodystrophy at injection site.
Storage	Store in multi dose containers in a refrigerator (2 to 8^{o}C). It should not be allowed to freeze.

Isophane Insulin

Schedule G

Indications	*Diabetes mellitus.*
Availability	**INJECTION** 40 and 80 IU/ml.
Dose	***Subcutaneous injection***

Adult and Child- Diabetes mellitus: according to individual's requirement.

Precautions See notes above; reduce dose in renal impairment; lactation.

Adverse Effects Hypoglycaemia in overdose; localized and rarely, generalized allergic reactions; lipodystrophy at injection site.

Storage Store in multi dose containers in a refrigerator (2 to 8°C). It should not be allowed to freeze.

Metformin*

Pregnancy Category-B

Schedule H

Indications *Diabetes mellitus.*

Availability **TABLETS** 250, 500, 850 mg, and 1g.

Dose ***Oral***

Adult- Diabetes mellitus: 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 or 850 mg every 12 h with or after food (max. 2g daily in divided doses).

Contraindications Renal impairment (withdraw if renal impairment suspected; Appendix 7d); 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 7c); anaemia; ketosis.

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); lactation (Appendix 7b); interactions (Appendix 6a, 6b, 6c); hepatic or renal disease (Appendix 7a); heart disease.

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 B_{12} absorption.

Storage Store protected from light and moisture.

Pioglitazone

Pregnancy Category-C

Schedule H

Indications	*Type 2 diabetes mellitus.*
Availability	**TABLETS** 15 and 30 mg.
Dose	***Oral***
	Type 2 diabetes mellitus: Adult- 15-30 mg once daily. Max. dose- 45 mg per day.
Contraindications	Hypersensitivity, type 1 diabetes, diabetic ketoacidosis, symptomatic or history of heart failure, children, lactation.
Precautions	Oedema, congestive heart failure, hepatic dysfunction, anaemia, concomitant oral contraceptives and hormone replacement therapy, pregnancy (Appendix 7c), interactions (Appendix 6c).
Adverse Effects	Oedema, headache, upper respiratory tract infection, GI disturbances, nausea, shortness of breath, weight gain, blurred vision, dizziness, arthralgia, impotence.
Storage	Store protected from heat, light and moisture at a temperature not exceeding 30°C.

24.4 Ovulation Inducers and Progestogens

24.4.1 Drugs for Ovulation Induction

The anti-estrogen, clomifene is used in the treatment of female infertility due to disturbances in ovulation. It induces gonadotrophin release by occupying estrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms. Patients should be carefully counselled and should be fully aware of the potential adverse effects, including a risk of multiple pregnancy (rarely, more than twins), of this treatment. Most patients who are going to respond will do so to the first course; 3 courses should be adequate; long-term cyclical therapy (more than 6 cycles) is not recommended as it may increase risk of ovarian cancer.

Clomifene*

Pregnancy Category-X

Schedule H

Indications	*Anovulatory infertility.*
Availability	**TABLETS** 25, 50 and 100 mg.
Dose	***Oral***
	Adult- Anovulatory infertility: 50 mg daily for 5 days, starting within 5 days of onset of menstruation, preferably on the second day, or at any time if cycles have ceased; a second course of 100 mg daily for 5 days may be given in the absence of ovulation.
Contraindications	Hepatic impairment (Appendix 7a); ovarian cysts; hormone dependent tumours or uterine bleeding of undetermined cause; pregnancy (exclude before treatment, Appendix 7c); hyperprolactinaemia; depression.
Precautions	Visual disturbances (discontinue and initiate eye examination) and ovarian hyperstimulation syndrome (discontinue treatment immediately); polycystic ovary syndrome (cysts may enlarge during treatment); uterine fibroids, ectopic pregnancy, incidence of multiple births increased (consider ultrasound monitoring); lactation (Appendix 7b).
Adverse Effects	Visual disturbances; ovarian hyperstimulation; hot flushes; abdominal discomfort; occasional nausea and vomiting; depression; insomnia; breast tenderness; headache; intermenstrual spotting; menorrhagia; endometriosis; convulsions; weight gain; rashes; dizziness and hair loss.

24.4.2 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.

Progestogens are also used in combined oral contraceptives and progestogen-only contraceptives.

Medroxyprogesterone* (Refer Page No. 465)

Norethisterone* (Refer Page No. 466)

Pregnancy Category-X

Schedule H

Indications	*Endometriosis; menorrhagia; severe dysmenorrhoea; contraception; premenstrual tension.*
Availability	**TABLET** 5 mg; **INJECTION** 1 ml ampoule (200 mg/ml).
Dose	***Oral*** **Adult-** Endometriosis: 10 mg daily starting on fifth day of cycle (increased if spotting occurs to 20 to 25 mg daily, reduce once bleeding has stopped). Menorrhagia: 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: 5 mg, 2 to 3 times daily from day 5 to 24 for 3 to 4 cycles.
Contraindications	Pregnancy (Appendix 7c); undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 7a); severe arterial disease; breast or genital tract cancer; porphyria; history in pregnancy of idiopathic jaundice, severe pruritus.
Precautions	Epilepsy; migraine; diabetes mellitus; hypertension; cardiac or renal disease and those susceptible to thromboembolism; depression; lactation (Appendix 7b).

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.

24.5 Oxytocics and Antioxytocics

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 β_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 β_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 h. 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 risk to the mother increases after 48 h and the response of the myometrium is reduced.

24.5.1 Oxytocics

Ergometrine

Pregnancy Category-C

Schedule H

Indications	*Prevention and treatment of postpartum and post-abortion haemorrhage in emergency situations and where oxytocin not available.*
Availability	**TABLETS** 0.125, 0.25 and 0.5 mg; **INJECTION** 5 ml ampoule (0.2 mg/ml).
Dose	***Oral***
	Adult and adolescent- Secondary postpartum haemorrhage: 400 µg 3 times daily for 3 days.
	Intramuscular injection

Adult and adolescent- Prevention and treatment of postpartum haemorrhage: when oxytocin is not available, 200 µg when the anterior shoulder is delivered or immediately after birth.

Slow intravenous injection

Adult and adolescent- Excessive uterine bleeding: 250 to 500 µg when the anterior shoulder is delivered or immediately after birth.

Contraindications Induction of labour, first and second stages of labour; vascular disease, severe cardiac disease especially angina pectoris; severe hypertension; hepatic impairment (Appendix 7a) and renal impairment; sepsis; eclampsia.

Precautions Cardiac disease, hypertension; multiple pregnancy (Appendix 7c); porphyria.

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.

Storage Tablets: Store protected from light at a temperature not exceeding 30°C. Injection: Store protected from light in a single dose container at a temperature not exceeding 30°C.

Oxytocin*

Pregnancy Category-C

Schedule H

Indications *Routine prevention and treatment of postpartum and post-abortion haemorrhage; induction of labour.*

Availability **INJECTION** 2 IU/2 ml and 5 IU/ml.

Dose ***Intravenous infusion***

Adult and adolescent- Induction of labour: initially 0.001 to 0.002 units/min increased in 0.001 to 0.002 units/min increments at intervals of 30 min until a max. of 3 to 4 contractions occur every 10 min; max. recommended rate 0.02 units/min.

Slow intravenous injection

Adult and adolescent- Prevention of postpartum haemorrhage: 5 units when the anterior shoulder is delivered or immediately after birth. Treatment of postpartum haemorrhage: 5-10 units.

Intramuscular injection

Adult and adolescent- Prevention of postpartum haemorrhage: 10 units when the anterior shoulder is delivered or immediately after birth.

10 units, followed in severe cases by slow intravenous infusion, a total of 40 units should be infused at a rate of 0.02-0.04 units/min; this should be started after the placenta is delivered.

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. 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.

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; uterine hyperactivity; major cephalopelvic disproportion, placental previa.

Precautions Induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant); mild to moderate pregnancy (Appendix 7c)-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 6a).

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; hypotension; sinus bradycardia; hematoma; fetal asphyxia.

Storage Store at a temperature not exceeding 30°C. Do not freeze.

Mifepristone + Misoprostol

Pregnancy Category-X

Schedule H

Indications *Medical termination of pregnancy of upto 49 days, cervical dilatation prior to surgical termination of pregnancy in the first trimester, therapeutic termination of pregnancy for medical reasons beyond the first trimester, labor induction in case of fetal death in utero.*

Availability **TABLET KIT** mifopristone 200 mg, misoprostol 200 µg.

Dose Mifepristone 200 mg orally followed 1 to 3 days latter by misoprostol 800 µg vaginally. Patients should return for followup visit after approximately 14 days after administration of mifepristone.

Contraindications Hypersensitivity to Mifepristone, Misoprostol or other prostaglandin; confirmed or suspected ectopic pregnancy (Appendix 7c); chronic adrenal failure; haemorrhagic disorders or concurrent anticoagulant therapy; inherited porphyria.

Precautions IUD in place; asthma, chronic obstructive pulmonary disease; alcoholism; prosthetic heart valve; infective endocarditis; interactions (Appendix 6c), pregnancy (Appendix 7c).

Adverse Effects Abdominal pain, diarrhoea, nausea, vomiting; fever, chills, uterine cramping; vaginal bleeding or spotting; Pelvic inflammatory disease.

24.5.2 Antioxytocics (Tocolytics)

Isoxsuprine

Pregnancy Category-C

Schedule H

Indications *Cerebral and peripheral vascular disorder; threatened abortion and premature labour; night cramps; habitual abortion.*

Availability **TABLETS** 10 and 20 mg; **INJECTION** 2 ml ampoule (5 mg/ml).

Dose ***Oral***

Premature labour and threatened abortion: initially 20 mg 6 hly after food, maintenance dose after improvement 10 mg thrice a day.

Intravenous injection/infusion

Premature labour and threatened abortion: 0.2 to 0.5 mg/min, adjust according to response, monitor BP and heart rate.

Contraindications Anaemia; heart disease, arterial hemorrhage; postpartum; premature detachment of placenta; hypersensitivity.

Precautions Blood disorders, bleeding episodes or allergies, pregnancy (Appendix 7c), lactation.

Adverse Effects Dizziness,nausea and vomiting; tachycardia, Irregular heart beat, hypotension, chest pain; flushed skin, rashes.

Terbutaline*

Pregnancy Category-B

Schedule H

Indications *Bronchial spasm in bronchial asthma and chronic bronchitis; emphysema; premature labour; lymphoma.*

Availability **TABLETS** 2.5 and 5 mg; **INJECTION** 1 ml ampoule (0.5 mg/ml), **NEBULISING SOLUTION** 10 mg/ml, **METERED DOSE INHALER (MDI)** 250 µg/puff .

Dose ***Oral***

Premature abortion: 2.5 to 5 mg thrice daily.

Acute bronchospasm: **Adult-** 2.5 to 5 mg thrice daily.

Subcutaneous, intramuscular or intravenous injection

Uncomplicated premature labour**: Adult-** 5 µg/min for 20min, increased every 20min in steps of 2.5 µg/min until contractions have ceased continue for 1 h then decreased every 20 min in steps of 205 µg/min to lowest dose that maintain suppression, max. dose 20 µg/min.

Severe bronchospasm: **Adult-** 250-500 µg, 4 times daily. **Child: >2 years**-10 µg/kg, max. dose- 300 µg.

Inhalation

Acute bronchospasm: **Adult/Child-** MDI- 250 or 500 µg every 4-6 h, max. dose- 2000 µg/24 h; As nebuliser- 5-10 mg inhaled 2-4times. **Child-** As nebuliser- 2-5 mg inhaled 2-4 times.

Contraindications

Cardiac disease; antepartum haemorrhage; intrauterine infection; intrauterine fetal death; placenta praevia; abruptio placenta; threatened miscarriage; cord compression; and eclampsia or severe pre-eclampsia; thyrotoxicosis; toxaemia.

Precautions

Suspected cardiovascular disease (such patients should be assessed by a cardiologist before initiating therapy), hypertension, mild to moderate pre-eclampsia, hyperthyroidism, and hypokalaemia (particular risk with potassium-depleting diuretics). It is important to monitor pulse rate (should not exceed 140 beats per min) and the patient's fluid and electrolyte status (avoid over-hydration-discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs). It should also be used with caution in diabetes-monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially with intravenous β_2 agonist); pregnancy (Appendix 7c).

Adverse Effects

Nausea, vomiting; pulmonary oedema; palpitation; tachycardia, arrhythmias, peripheral vasodilation; headache, tremor, hyperglycaemia, hypokalaemia, muscle cramps and tension and hypersensitivity reactions (including angioedema, urticaria, rash, bronchospasm, hypotension, and collapse).

Storage

Tablet: Store protected from light and moisture. Injection: Store protected from light in a single dose container.

24.6 Thyroid Hormones and Antithyroid Drugs

Thyroid Drugs:

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 cardiostimulatory 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.

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 lactation 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.

Carbimazole*

Pregnancy Category-D

Schedule H

Indications	*Thyrotoxicosis; Grave's disease.*
Available:	**TABLETS** 5 and 10 mg.
Dose	***Oral***
	Initially 15 to 45 mg daily in 4 divided doses depending upon severity. Maintenance dose 25 to 50 mg for 1 year.
Contraindications	Nodular goitre; subacute thyroiditis, postpartum painless thyroiditis.
Precautions	Liver disorders; pregnancy (Appendix 7c), lactation; neutropenia.
Adverse Effects	Nausea, mild gastro-intestinal disturbances; headache; rashes and pruritus, arthralgia; rarely, myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis); vasculitis; cholestatic jaundice, hepatic necrosis.
Storage	Store protected from light and moisture at a temperature not exceeding 30°C.

Iodine* (Refer Page No. 608)

Pregnancy Category-D

Indications	*Hypothyroidism; sporotrichosis.*
Available:	**COLLOIDAL IODINE** 8 mg/5 ml.
Dose	5 to 10 ml diluted in water 3 times a day.
Contraindications	Lactation (Appendix 7b), tuberculosis, bronchitis, asthma, hyperkalaemia, acne vulgaris.

Precautions Pregnancy (Appendix 7c), children; not for long-term treatment; cardiac disease, interactions (Appendix 6c).

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; eosinophilia, hypothyroidism, abdominal pain, arrhythmia.

Storage Store in ground glass stoppered container or earthenware container with waxed bungs.

Levothyroxine*

Pregnancy Category-A

Schedule H

Indications *Hypothyroidism.*

Availability **TABLETS** 50 and 100 µg.

Dose ***Oral***

Adult- Hypothyroidism: Initially 50 to 100 µg daily (25 to 50 µg for those over 50 years) before breakfast, increased by 25 to 50 µg every 3 to 4 weeks until normal metabolism maintained (usual maintenance dose, 100 to 200 µg daily); where there is cardiac disease, initially 25 µg daily or 50 µg on alternate days, adjusted in steps of 25 µg every 4 weeks.

Child- Congenital hypothyroidism and juvenile myxoedema; Up to 1 month: initially 5 to 10 µg/kg daily. Over 1 month: initially 5 µg/kg daily, adjusted in steps of 25 µg every 2 to 4 weeks, until mild toxic symptoms appear, then reduce dose slightly.

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 7c), lactation; interactions (Appendix 6c, 6d).

Adverse Effects

Anginal pain, arrhythmias, palpitations, tachycardia, skeletal muscle cramps; diarrhoea, vomiting; tremors; restlessness excitability, insomnia, headache, flushing, sweating; excessive loss of weight and muscular weakness; heat intolerance.

Storage

Store protected from light and moisture.

28. Psychotherapeutic Drugs

28.1 Antianxiety Agents and Drugs Used In Sleep Disorders

A sedative drug decreases activity, moderates excitement and calms the recipient, whereas, a hypnotic drug produces drowsiness and facilitates the onset and maintenance of a sleep state that resembles natural sleep. 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 hour 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.

Alprazolam*

Pregnancy Category-D

Schedule H

Indications *Anxiety disorders; panic attacks.*

Availability **TABLETS** 0.25, 0.5 and 1 mg.

Dose ***Oral***

Adult- 0.25 to 0.5 mg daily 2 to 3 times a day.

Child- Not recommended.

Contraindications Respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; severe hepatic impairment; not for chronic psychosis; should not be used alone in depression or in anxiety with depression; avoid injections containing benzyl alcohol in neonates; narrow angle glaucoma, hypersensitivity.

Precautions Respiratory disease; muscle weakness and myasthenia gravis; history of drug or alcohol abuse; marked personality disorder; pregnancy (Appendix 7c), lactation; reduce dose in elderly and debilitated and in hepatic impairment, renal impairment; avoid prolonged use (and abrupt withdrawal thereafter); interactions (Appendix 6a); periodic blood count; liver function test.

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Adverse Effects Drowsiness and lightheadedness on the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally: headache, vertigo, hypotension, salivation changes, gastro-intestinal disturbances, visual disturbances, dysarthria, tremor, changes in *libido,* incontinence, urinary retention; blood disorders and jaundice reported; skin reactions; rarely, apnoea and insomnia.

Storage Store protected from light.

Diazepam* (Refer Page No. 57 and 420)

Pregnancy Category-D

Schedule H

Indications

Short-term treatment of anxiety and insomnia; status epilepticus, recurrent seizures; febrile convulsions, adjunct in acute alcohol withdrawal; premedication; agitation.

Availability

TABLETS 2.5, 5 and 10 mg; **INJECTION** 10 mg/2 ml; **CAPSULES** 10 and 15 mg.

Dose

Oral

Adult- Anxiety: 2 mg 3 times daily, increased if necessary to 15 to 30 mg daily in divided doses. Insomnia: 5 to 15 mg at bedtime.
Child- Oral 1-2.5 mg, 3 or 4 times daily (Not for use under 6 months).

Elderly or debilitated- Anxiety: half adult dose.

Contraindications

Respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis; hypersensitivity.

Precautions

Respiratory disease; muscle weakness; history of alcohol or drug abuse; marked personality disorder; lactation (Appendix 7b); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 7a); renal impairment; avoid prolonged use and abrupt withdrawal; porphyria; interactions (Appendix 6a, 6c); pregnancy (Appendix 7c); liver function test to be done, least amount of drug should be given in patients in whom depression accompanies anxiety and suicidal tendencies.

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

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; reduces reflexes; jaundice; psychological dependence; physiological dependence, respiratory arrest.

Storage Tablet: Store protected from light. Injection: Store in single dose or multi dose container protected from light.

Lorazepam*

Pregnancy Category-D

Schedule H

Indications *Anxiety disorders.*

Availability **TABLETS** 0.5, 1, 2, 2.5 and 3 mg
INJECTIONS 2 ml ampoule (2 mg/ml).

Dose 2 to 6 mg/day given in divided doses, initial dose of 2 to 3 mg/day given twice or thrice a day.

Elderly or debilitated patients: Initial dosage of 1 to 2 mg/day in divided doses.

Contraindications Severe hepatic impairment; respiratory depression; acute narrow angle glaucoma; pregnancy (Appendix 7c), lactation.

Precautions Hepatic dysfunction; impaired ability to drive or operate machinery; interactions (Appendix 6a).

Adverse Effects Nausea and vomiting, dizziness; weakness; blurred vision; vertigo.

Nitrazepam

Pregnancy Category-D

Schedule H

Indications *Insomnia; epilepsy, vertigo, infantile spasm.*

Availability **CAPSULES/TABLETS** 2.5, 5 and 10 mg.

Dose ***Oral***

Insomnia- 5 to 10 mg at bed time.

Child

Infantile spasm- 125 µg/kg twice daily, gradually increase to 250-500 µg/kg twice daily.

Contraindications Respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; severe hepatic impairment; sleep apnoea syndrome; not for use alone to treat depression (or anxiety associated with depression) or chronic psychosis.

Precautions Muscle weakness and myasthenia gravis; history of drug or alcohol abuse; marked personality disorder; pregnancy (Appendix 7c), lactation; reduce dose in elderly and debilitated, and in hepatic impairment and renal impairment; avoid prolonged use (and abrupt withdrawal thereafter); porphyria; interactions (Appendix 6a); blood count, increased salivation.

Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Adverse Effects Drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia may occur; dependence; aggression, anaphylaxis, dysarthria, blurred vision, slurred speech.

Storage Store protected from light and moisture.

Zolpidem

Pregnancy Category-C

Schedule H

Indications *Short term management of insomnia.*

Availability **TABLETS** 5 and 10 mg, 6.25 and 12.5 mg **CR**, **CAPSULES** 5 and 10 mg.

Dose **Adult-** 10 mg immediately before bed time, maximum 10 mg/day, controlled release tablets 12.5 mg immediately before bed time.

Elderly- 5 mg before bed time.

Contraindications Severe hepatic insufficiency.

Precautions Myasthenia gravis; depressed patients; hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle; obstructive sleep apnoea, compromised respiratory function; pregnancy (Appendix 7c), lactation, interactions (Appendix 6a,6c).

Adverse Effects Abnormal thinking, behaviour changes, and complex behaviours, withdrawal effects, CNS-depressant effects, ataxia, confusion, diplopia, euphoria; hepatitis; anaphylactic reactions.

28.2 Antidepressants

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 max. 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 5 years and possibly indefinitely). Lithium may be used as an alternative for maintenance treatment. 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*

Pregnancy Category-C

Schedule H

Indications

Moderate to severe depression, migraine prophylaxis; tension, headache, enuresis.

Availability

TABLETS 10, 25, 50 and 75 mg; **INJECTION** 10 ml ampoule (10 mg/ml).

Dose

Oral

Adult- Initially 75 mg (adolescents 30 to 75 mg) daily in divided doses or as a single dose at bed time increased gradually as necessary to 150 to 200 mg daily. Prophylaxis of migraine: 10-75 mg at night.

Child- Under 16 years; not recommended.

Contraindications

Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria; glaucoma, prostatic hypertrophy.

Precautions

Cardiac disease (see Contraindications above); history of epilepsy; lactation (Appendix 7b); elderly; hepatic impairment (Appendix 7a); thyroid disease; pheochromocytoma; 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 6a, 6b, 6c); pregnancy (Appendix 7c); pre-existing haematological disorder, abrupt disorientation.

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

Adverse Effects Sedation; dry mouth; blurred vision (disturbance of accommodation, increased intraocular pressure); constipation; nausea; difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope; sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity); 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.

Escitalopram

Pregnancy Category-C

Indications *Depression, obsessive compulsive disorder, anxiety disorder, panic disorder.*

Availability **TABLETS** 5, 10 and 20 mg.

Dose Initially 10 mg once daily. Maximum- 20 mg daily.

Contraindications Concomitant use with MAO Inhibitors, thioridazine.

Precautions History of panic disorder or seizure disorders, renal impairment, hepatic impairment, work requiring mental alertness, concomitant use of escitalopram with other SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs) or tryptophan, interactions (Appendix 6c), pregnancy (Appendix 7c).

Adverse Effects Insomnia, nausea, ejaculation disorder.

Fluoxetine*

Pregnancy Category-C

Schedule H

Indications *Major depression (including pediatric depression); obsessive-compulsive disorder (in both adult and pediatric populations); bulimia nervosa; anorexia nervosa; panic disorder and premenstrual dysphoric disorder; depression illness, Parkinson's disease.*

Availability **TABLETS** 10, 20, 40 and 60 mg; **CAPSULES** 10, 20 and 60 mg.

Dose ***Oral***

20 mg/day initially (max 60 mg).

Contraindications Should not be used if the patient enters a manic phase; renal failure, hypersensitivity.

Precautions Should be used with caution in patients with epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastro-intestinal bleeding), and if used with other drugs that increase the risk of bleeding, hepatic impairment (Appendix 7a), renal impairment, pregnancy (Appendix 7c), and lactation. They should also be used with caution in those receiving concurrent electroconvulsive therapy (prolonged seizures reported with fluoxetine). The risk of suicidal behaviour is possibly higher in young adults, calling for close monitoring of those receiving SSRIs. SSRIs may also impair performance of skilled tasks (e.g. driving), interactions (Appendix 6a, 6c).

Adverse Effects Gastro-intestinal effects (dose-related and fairly common-include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation), anorexia with weight loss (increased appetite and weight gain also reported) and hypersensitivity reactions including rash (consider discontinuation-may be sign of impending serious systemic reaction, possibly associated with vasculitis), urticaria, angioedema, anaphylaxis, arthralgia, myalgia and photosensitivity; other side-effects include dry mouth, nervousness,anxiety, headache, insomnia, tremor, asthenia, hallucinations, drowsiness, convulsions, galactorrhoea, sexual dysfunction, urinary retention, sweating, hypomania or mania, movement disorders and dyskinesias, visual disturbances, hyponatraemia; serum sickness, elevation of liver enzymes.

Storage Store protected from moisture.

Imipramine*

Pregnancy Category-D

Schedule H

Indications *Panic attacks; chronic pain; nocturnal enuresis; Kleine-Levin syndrome; depression, hyperactivity, attention deficit disorder.*

Availability **TABLETS** 5, 25 and 75 mg; **CAPSULES** 25 and 75 mg.

Dose ***Oral***

75 mg/day initially, usual dose 100 to 200 mg daily.

Child- <6 years: not recommended, 6-12 years: 25 mg at bed time, >12 years: 50 mg at bed time.

Contraindications

Recent myocardial infarction, arrhythmias (particularly heart block), not indicated in manic phase, severe liver disease; epilepsy, mania, narrow angle glaucoma, hypersensitivity.

Precautions

Cardiac disease (particularly with arrhythmias), history of epilepsy, pregnancy (Appendix 7c), lactation, elderly, hepatic impairment, interactions (Appendix 6a), thyroid disease, pheochromocytoma, history of mania, psychoses (may aggravate psychotic symptoms), susceptibility to angle-closure glaucoma, history of urinary retention, concurrent electroconvulsive therapy; if possible avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension), see surgery; porphyria; for additional nocturnal enuresis warnings; acetylsalicylic acid hypersensitivity.

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Adverse Effects

Dry mouth, sedation, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty with micturition; cardiovascular sideeffects (such as ECG changes, arrhythmias, postural hypotension, tachycardia, syncope, particularly with high doses); sweating, tremor, rashes and hypersensitivity reactions (including urticaria, photosensitivity), behavioural disturbances (particularly children), hypomania or mania, confusion or delirium (particularly elderly), headache, interference with sexual function, blood sugar changes; increased appetite and weight gain (occasionally weight loss); endocrine side-effects such as testicular enlargement, gynaecomastia, galactorrhoea; also convulsions, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (see Hyponatraemia and Antidepressant Therapy), abnormal liver function tests (jaundice); impairment of memory, cutaneous vasculitis.

Storage

Store protected from light.

28.3 Antipsychotics

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 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 h 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 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 drugs. 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. 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*

Pregnancy Category-C

Schedule H

Indications

Schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety; psychosis, mania, hiccups.

Availability

TABLETS 25, 50 and 100 mg; **SYRUP** 60 ml (25 mg/5 ml); **INJECTION** 2 ml ampoule (25 mg/ml).

Dose

Oral

Adult- Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour and severe anxiety (adjuvant): initially 25 mg 3 times daily (or 75 mg at night) adjusted to response to usual maintenance dose of 100-300 mg daily (but up to 1.2g daily may be required in psychosis).

Elderly or debilitated- Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour and severe anxiety (adjunct): one-third to one-half adult dose.

Child- Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour and severe anxiety (adjunct); (for childhood schizophrenia and autism) 1 to 5 years: 500 µg/kg every 4-6 h (max. 40 mg daily). 6 to 12 years: one-third to one-half adult dose (max. 75 mg daily).

Deep intramuscular injection

Adult- Relief of acute symptoms: 25 to 50 mg every 6 to 8 h.

Child- Relief of acute symptoms: 500 µg/kg every 6 to 8 h (1 to 5 years: max. 40 mg daily. 6 to 12 years: max. 75 mg daily).

Contraindications

Impaired consciousness due to CNS depression; bone-marrow depression; pheochromocytoma; epilepsy, narrow angle glaucoma, Parkinson's disease; depressed level of consciousness.

Precautions

Cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 7c), lactation (Appendix 7b), renal and hepatic impairment (avoid if severe; Appendices 7a), 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 min after intramuscular injection; interactions (Appendix 6a, 6c); extreme heat, alcohol withdrawal, peptic ulcer.

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

Adverse Effects

Extrapyramidal symptoms and on prolonged administration, occasionally potentially irreversible tardive dyskinesias (see 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; seizures, temperature disorder, hyperprolactinemia, ocular complication.

Storage

Store protected from light.

Fluphenazine

Pregnancy Category-C

Schedule H

Indications

Maintenance treatment of schizophrenia and other psychoses; mania, postoperative nausea.

Availability

TABLET 1 mg; **INJECTION** 1 ml ampoule (25 mg/ml).

Dose

Deep intramuscular injection into gluteal muscle.

Adult- Maintenance in schizophrenia and other psychoses: test dose of 12.5 mg, then after 4 to 7 days, 12.5 to 100 mg repeated at intervals of 2 to 5 weeks, adjusted according to the response.

Elderly- Maintenance in schizophrenia and other psychoses: test dose of 6.25 mg, then after 4 to 7 days, 12.5 to 100 mg repeated at intervals of 2 to 5 weeks, adjusted according to the response.

Child- Maintenance in schizophrenia and other psychoses: not recommended.

Contraindications

Children; confusional states; impaired consciousness due to CNS depression; parkinsonism; intolerance to antipsychotics; depression; bone-marrow depression; pheochromocytoma; blood dyscrasias, coma, brain damage.

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 7c), lactation (Appendix 7b); renal and hepatic impairment (avoid if severe; Appendices 7a), 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 6a, 6c); alcohol withdrawal, extreme heat.

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

Adverse Effects

As for Chlorpromazine (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; tardive dyskinesia, neurological disturbances, blood dyscrasias.

Storage

Store protected from light.

Haloperidol*

Pregnancy Category-C

Schedule H

Indications

Schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety; agitation, psychosis, neuroleptanalgesia.

Availability

TABLETS 1.5, 5, 10 and 20 mg; **LIQUID** 30 ml (25 mg/ml); **INJECTION** 5 ml ampoule (5 mg/ml).

Dose

Oral

Adult-Schizophrenia and other psychoses, mania, psychomotor agitation and violent behaviour and severe anxiety (adjuvant): initially 1.5 to 3 mg 2 to 3 times daily or 3 to 5 mg 2 to 3 times daily in severely affected or resistant patients (up to 30 mg daily in resistant schizophrenia).

Elderly or debilitated-Schizophrenia and other psychoses, mania, psychomotor agitation and violent behaviour and severe anxiety (adjuvant): initially half adult dose.

Child-Schizophrenia and other psychoses, mania, psychomotor agitation and violent behaviour and severe anxiety (adjuvant): initially 25 to 50 µg/kg daily in 2 divided doses (max. 10 mg daily).

Intramuscular injection

Adult- Acute psychotic conditions: initially 2 to 10 mg, subsequent doses every 4 to 8 h according to response (up to every h if necessary) to max. of 18 mg; severely disturbed patients may require initial dose of up to 18 mg.

Elderly or debilitated- Acute psychotic conditions: initially half adult dose.

Child- Acute psychotic conditions: not recommended.

Contraindications

Impaired consciousness due to CNS depression; bone-marrow depression; pheochromocytoma; porphyria; basal ganglia disease; parkinsonism, thyrotoxicosis, cardiac arrhythmia, depression, close angle glaucoma.

Precautions Cardiovascular and cerebrovascular disorders; respiratory disease; parkinsonism; epilepsy; acute infections; pregnancy (Appendix 7c), lactation (Appendix 7b); renal and hepatic impairment (avoid if severe; Appendices 7a), 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, hypocalcaemia, 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 min after intramuscular injection; interactions (Appendix 6a, 6c); photosensitisation, peptic ulcers.

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

Adverse Effects As for Chlorpromazine (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.

Storage Store protected from light.

Olanzapine*

Pregnancy Category-C

Schedule H

Indications *Schizophrenia, acute mania episodes in bipolar disorder.*

Availability **TABLETS** 2.5, 5, 7.5, 10, 15 and 20 mg.

Dose Schizophrenia: initial 5-10 mg, usual dose is 10-20 mg. Acute maniac episodes in bipolarillness: 10-15 mg/day.

Precautions Impaired renal, hepatic and cardiovascular function; prostratic hypertrophy; paralytic ileus; parkinsonism; blood dyscrasias; myelosupression; seizures; dementia; pregnancy (Appendix 7c).

Adverse effects Postural hypotension, dizziness, constipation, weight gain, agitation, insomnia, akathesia, tremors, personality disorder, oedema, increases appetite, antimuscarinic effects, hallucination, bradycardia.

Trifluoperazine

Pregnancy Category-C

Schedule H

Indications

Schizophrenia, non-psychotic anxiety, acute psychosis.

Availability

TABLETS 1, 2, 5 and 10 mg;
INJECTION 10 ml ampoule (10 mg/10 ml), 5 ml ampoule (2 mg/ml).

Dose

Oral

Schizophrenia and Psychosis:
Adult and child over 12 years- Initially 5 mg twice daily, increase by 5 mg daily to 15-20 mg daily after 1 week and then at intervals of 3 days, according to response.

Elderly- reduce initial dose by atleast half.

Anxiety management:
Adult- 1-2 mg twice daily. Max.- 6 mg daily.

Child- 3 to 5 years, Max.- 1 mg daily in divided dose.

Child- 6 to 12 years, Max.- 4 mg daily.

Elderly- reduce initial dose by atleast half.

Antiemetic: 2–4 mg daily in divided doses or as a single dose of a modified-release preparation; max. 6 mg daily.

Child- 3–5 years up to 1 mg daily, 6–12 years up to 4 mg daily.

Parenteral

Psychosis:
Adult- 1-2 mg by deep i.m injection, repeat every 4-6 h, if necessary.

Child- 1 mg by deep i.m injection, once or twice daily.

Contraindications

Hypersensitivity to phenothiazines; bone marrow depression; blood dyscrasias; pre-existing CNS depression and coma; pheochromocytoma.

Precautions

Myasthenia gravis; renal and hepatic impairment; benign prostatic hyperplasia; glaucoma; epilepsy; exposure to extreme heat or phosphorous insecticides; peptic ulcer, Parkinson's disease, interactions (Appendix 6a), pregnancy (Appendix 7c).

Adverse effects

Extrapyramidal symptoms particularly in children, elderly and debilitated patients more frequently at doses exceeding 6 mg daily; pancytopenia, thrombocytopenia; hyperpyrexia; dizziness, anorexia; insomnia; dry mouth; blurred vision; postural hypotension.

Storage

Injection: Store protected from light. Tablets: Store protected from light and moisture.

28.4 Drugs for 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 6c). 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 if benefit persists.

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 h 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).

Carbamazepine* (Refer Page No. 55)

Pregnancy Category-D

Schedule H

Indications — *Prophylaxis of bipolar disorder unresponsive to or intolerant of lithium; epilepsy, trigeminal neuralgia.*

Availability — **TABLETS** 100, 200 and 400 mg Plain; 100 mg (DT) **SYRUP** 100 mg/5 ml.

Dose — ***Oral***

Adult- Initially 400 mg daily in divided doses increased until symptoms are controlled to a max. of 1.6g daily: usual maintenance range 400 to 600 mg daily.
Trigeminal neuralgia: initially 100 mg twice daily, maintenance dose is 400-800 mg/day.

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

Precautions — Hepatic impairment (Appendix 7a); renal impairment; cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; (neural tube screening); lactation (Appendix 7b); avoid sudden withdrawal; interactions (Appendix 6b, 6c, 6d); pregnancy (Appendix 7c); patients on anticoagulants.

Patients or their caretakers 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).

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

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; exfoliative dermatitis,ankle swelling.

Lithium Carbonate*

Pregnancy Category-D

Schedule H

Indications

Treatment and prophylaxis of mania, prophylaxis of bipolar disorder and recurrent depression; ADH secretion syndrome, psychosis.

Availability

TABLETS 150, 200, 300 and 400 mg; **CAPSULES** 150 and 300 mg.

Dose

Oral

Adult-Treatment of mania: initially 0.6 to 1.8g daily.

Prophylaxis of mania, bipolar disorder and recurrent depression: initially 0.6 to 1.2g daily.

Elderly-Treatment of mania: initially 300 to 900 mg daily.

Prophylaxis of mania, bipolar disorder and recurrent depression: initially 300 to 900 mg daily.

Contraindications

Renal impairment; cardiac insufficiency; conditions with sodium imbalance such as Addison's disease; fetal goiter; heart failure; psoriasis; kidney infection; hypothyroidism.

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); lactation (Appendix 7b); pregnancy (Appendix 7c); elderly (reduce dose); diuretic treatment, myasthenia gravis; surgery; if possible, avoid abrupt withdrawal (see notes above); interactions (Appendix 6c, 6d); kidney, thyroid and heart function test, children and adolescents.

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.

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; sinus bradycardia, leukocytosis, glycosuria, weight gain.

Storage

Store protected from moisture.

28.5 Drugs Used for 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

Pregnancy Category-C

Schedule H

Indications	*Phobic and obsessional states; panic attacks; blocking replacement, cataplexy, chronic diarrhoea.*
Availability	**TABLETS** 10, 25, 50 and 75 mg; **CAPSULES** 10 and 25 mg.
Dose	***Oral*** **Adult-**Initially 25 mg daily, usually at bedtime increased over 2 weeks to 100 to 150 mg daily. **Elderly-** Initially 10 mg daily, usually at bedtime increased over 2 weeks to 100 to 150 mg daily. **Child-** Not usually recommended.
Contraindications	Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; children; porphyria; narrow angle glaucoma, urinary retention.
Precautions	Cardiac disease (see Contraindications above), history of epilepsy; lactation (Appendix 7b); pregnancy (Appendix 7c); elderly; hepatic impairment (Appendix 7a); thyroid disease; pheochromocytoma; 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 6a, 6b); decreased urine output, breathing problem.

	May impair ability to perform skilled tasks, for example operating machinery, driving.
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; extrapyramidal syndrome, bone marrow depression, hypertension, stroke.
Storage	Store protected from light and moisture.

Fluoxetine* (Refer Page No. 572)

28.6 Drugs Used in Substance Dependence Programme

Methadone

Pregnancy Category-C

Schedule H

Indications — *Adjunct in treatment of opioid dependence.*

Availability — **TABLETS** 5, 10, 20 and 40 mg; **SYRUP** 5 mg/ml.

Dose — ***Oral***

20-30 mg initially followed by increase of 5 to 10 mg until a dose of 60 to 100 mg/day is achieved.

Contraindications — Avoid in acute respiratory depression, acute alcoholism and where risk of paralytic ileus; also avoid in raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in pheochromocytoma (risk of pressor response to histamine release).

Precautions — Hypotension, hypothyroidism, asthma (avoid during attack) and decreased respiratory reserve, prostatic hypertrophy; pregnancy (Appendix 7c), lactation; may precipitate coma in hepatic impairment (Appendix 7a) (reduce dose or avoid but many such patients tolerate morphine well); reduce dose or avoid in renal impairment, elderly and debilitated (reduce dose); convulsive disorders, dependence (severe withdrawal symptoms if withdrawn abruptly); use of cough suppressants containing opioid analgesics not generally recommended in children and should be avoided altogether in those under at least 1 year; interactions (Appendix 6a, 6c, 6d); CNS depression, ulcerative colitis, gastrointestinal surgery, bradyarrhythmia, pulmonary diseases.

Adverse Effects

Nausea and vomiting (particularly in initial stages), constipation and drowsiness; larger doses produce respiratory depression; hypotension, and muscle rigidity; other side-effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitation, postural hypotension, hypothermia, hallucinations, dysphoria, mood changes, dependence, miosis, decreased *libido* or potency, rashes, urticaria and pruritus; seizures, exacerbation of asthma, itching, pulmonary oedema.

Storage

Store protected from light and moisture.

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30. Vitamins, Minerals and Antianaemic Drugs

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 D_2) and pyridoxine (vitamin B_6) 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 B_1) is used orally for deficiency due to 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 B_2) 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 B_6) 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. **Nicotinic acid** inhibits the synthesis of cholesterol and triglyceride and is used in some hyperlipidaemias. Nicotinic acid and **nicotinamide** are used to prevent and treat nicotinic acid deficiency (pellagra). Nicotinamide is generally preferred as it does not cause vasodilation. **Hydroxocobalamin** is the form of vitamin B_{12} used to treat vitamin B_{12} deficiency due to dietary deficiency or malabsorption (see chapter 13.1).

Folic acid is essential for the synthesis of DNA and certain proteins. Deficiency of folic acid or vitamin B_{12} is associated with megaloblastic anaemia. Folic acid should not be used in undiagnosed megaloblastic anaemia unless vitamin B_{12} is administered concurrently, otherwise neuropathy may be precipitated (see chapter 13.1). Supplementation with folic acid 500 µg daily is recommended for women of child-bearing potential in order to reduce the risk of serious neural tube defects in their offspring.

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 D_2) and **cholecalciferol** (vitamin D_3). 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

cholecalciferol (vitamin D_3) in their skin from the precursor 7-dehydrocholesterol in response to ultraviolet light.

Vitamin K is necessary for the production of blood clotting factors.

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 µg daily (200 µg daily in pregnant and lactation women); in children the recommended intake of iodine is 50 µg daily for infants under 1 year, 90 µg daily for children aged 2-6 years, and 120 µg 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 witheld from pregnant women. Control of iodine deficiency largely depends upon salt iodization with potassium iodide or potassium iodate and through dietary diversification. In areas where iodine deficiency disorders are moderate to severe, iodized oil given either before or at any stage of pregnancy is found to be beneficial.

Sodium fluoride: Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect. Where the natural fluoride content of the drinking water is significantly less than 1 mg per litre, artificial fluoridation is the most economical method of supplementing fluoride intake. Daily administration of fluoride tablets or drops is a suitable alternative, but systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply; they are not advisable when the water contains more than 700 µg per litre. In addition, infants need not receive

fluoride supplements until the age of 6 months. Dentifrices which incorporate Sodium fluoride are a convenient source of fluoride. Individuals who are either particularly caries prone or medically compromized may be given additional protection by the use of fluoride rinses or by application of fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied on a regular basis under professional supervision; extreme caution is necessary to prevent the child from swallowing any excess.

Ascorbic Acid (Vitamin C)*

Pregnancy Category-A, C

Indications — *Prevention and treatment of scurvy.*

Availability — **TABLETS** 100 and 500 mg; **DROP** 100 mg/ml; **INJECTION** 5 ml ampoule (100 mg/ml)

Dose — ***Oral***

Adult and child- Prophylaxis of scurvy: 25 to 75 mg daily. Treatment of scurvy: 0.5 to 1.5g/day.

Contraindications — Hyperoxaluria.

Precautions — Acetylsalicylic acid hypersensitivity; G-6-PD deficiency; large doses may cause renal calcium oxalate calculi; pregnancy (Appendix 7c).

Adverse Effects — Gastrointestinal disturbances reported with large doses; failure of conception; kidney oxalate stones.

Storage — Store protected from light and moisture. Avoid contact with metals.

Calcium Carbonate + Vitamin D_3

Pregnancy Category-A

Indications — *Prevention and treatment of osteoporosis and osteomalacia, nutritional supplement.*

Availability — **TABLET** Vitamin D_3 250 IU + Calcium 500 mg **SUSPENSION** 200 ml (Calcium 100 mg+Vitamin D_3 200 IU/5 ml).

Dose — ***Oral***

Adult
Calcium 1000 -1300 mg daily
Vitamin D_3 200 - 800 IU daily.

Contraindications Hypersensitivity to any of the components, hypercalcaemia and/or hypercalciuria, nephrolithiasis, hypervitaminosis.

Precautions Renal impairment, impaired calcium absorption in achlorhydria, risk of hypercalcaemia and hypercalciuria in hypoparathyroid patients receiving high doses of vitamin D; interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Constipation, flatulence, nausea, abdominal pain and diarrhoea; pruritus, rash and urticaria.

Calcium Gluconate*

Indications *Hypocalcaemic tetany; cardiopulmonary bypass.*

Availability **TABLETS** 250 and 500 mg; **INJECTION** 10 ml (1g/10 ml).

Dose ***Slow intravenous injection and continuous intravenous infusion***

Adult- Hypocalcaemic tetany: 1g (2.2 mmol) by slow intravenous injection, followed by continuous intravenous infusion of about 4g (8.8 mmol) daily.

Contraindications Conditions associated with hypercalcaemia and hypercalciuria (for example some forms of malignant disease).

Precautions Monitor plasma calcium concentration; renal impairment; interactions (Appendix 6c); diarrhoea, parathyroid disease; stomach trouble.

Adverse Effects Mild gastrointestinal disturbances; bradycardia, arrhythmias, hypotension; irritation at injection site; soft tissue calcification; nephrocalcinosis, renal calculi.

Ergocalciferol (Vitamin D_2)*

Pregnancy Category-C

Indications *Prevention of vitamin D deficiency; vitamin D deficiency caused by malabsorption or chronic liver disease; hypocalcaemia of hypoparathyroidism; osteomalacia; osteoporosis.*

Availability **CAPSULES** 0.25 and 1 mg (50,000 IU).

Dose ***Oral***

Adult and child- Prevention of vitamin D deficiency: 10 µg (400 units) daily.

Contraindications Hypercalcaemia; metastatic calcification.

Precautions Ensure correct dose in infants; monitor plasma calcium at weekly intervals in patients receiving high doses or those with renal impairment; nausea and vomiting-may indicate overdose and hypercalcaemia; lactation (Appendix 7b); interactions (Appendix 6a); pregnancy (Appendix 7c).

Adverse Effects Symptoms of overdosage include anorexia; lassitude; nausea and vomiting, diarrhoea, weight loss; polyuria; sweating; headache; thirst, vertigo and raised concentrations of calcium and phosphate in plasma and urine; tissue calcification may occur if dose of 1.25 mg continued for several months; cardiac arrhythmia; hypervitaminosis D; over psychosis; paralytic ileus.

Storage Store protected from light in a hermetically sealed container.

Iodine* (Refer Page No. 505)

Pregnancy Category-D

Indications *Prevention and treatment of iodine deficiency; thyrotoxicosis; hyperthyroidism.*

Availability **CRYSTALS BULK**.

Dose ***Oral***

Adult- Endemic moderate to severe iodine deficiency: during pregnancy and one year postpartum, 300 to 480 mg once a year or 100 to 300 mg every 6 months; women of child-bearing age, 400 to 960 mg once a year or 200 to 480 mg every 6 months. Iodine deficiency; 400 mg, during pregnancy, single dose of 200 mg.

Child- Iodine deficiency: infant under 1 year, single dose 100 mg; 1 to 5 years, 200 mg once a year; above 6 years 400 mg once a year.

Intramuscular injection

Endemic moderate to severe iodine deficiency: women of child-bearing age, including any stage of pregnancy, 480 mg once each year; Iodine deficiency: 380 mg (if aged over 45 or with nodular goiter then 76 mg).

Child- Iodine deficiency; 380 mg but for infant up to 1year, 190 mg.

Contraindications Lactation (Appendix 7b); bronchitis; goitre; hyperkalaemia; asthma; acne vulgaris; tuberculosis.

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 7c); acute iodide toxicity; cardiac toxicity; interactions (Appendix 6c).

Adverse Effects Hypersensitivity reactions; goitre and hypothyroidism; hyperthyroidism; bronchitis; eosinophilia; rashes; headache; salivation.

Iron Salts* (Refer Page No. 618)

Methylcobalamin

Pregnancy Category-A

Indications *To prevent neurological disorder in patients with neuropathy due to diabetes, alcohol or other drug induced neuropathies.*

Availability **TABLETS** 500 µg, **INJECTION** 500 µg/ml and 0.2 mg/vial.

Dose Initially 1000 µg 3 times a day for 2 weeks, thereafter 1000 µg every 3 months by intramuscular injection in case of pernicious anaemia and other macrocytic anaemia. Incase with neurological involvement, initially 1 µg on alternate days. Until no further improvement, thereafter 1000 µg every 2 to 3 months. Prophylaxis: 1000 µg every 2 to 3 months.

Contraindications Hypersensitivity.

Precautions Allergies; pregnancy (Appendix 7c).

Adverse Effects Itching; anaphylactic shock with parenterals, pulmonary oedema; CHF; polycythemia vera.

Storage **INJECTION** Store in single-dose or multi-dose container protected from light in a refrigerator (2° to 8°C). Do not freeze.

Tablet: Store protected from light and moisture.

Nicotinamide*

Pregnancy Category-A

Indications *Treatment of pellagra; hartnup disease; inflammatory skin disease.*

Availability **TABLET** 50 mg.

Dose ***Oral***

Adult- Treatment of pellagra: up to 500 mg daily in divided doses.

Precautions Avoid contact with eyes and mucous membranes (including nose and mouth); reduce frequency of application if excessive dryness, irritation or peeling; history of heart disease; insulin dependent diabetes; pregnancy (Appendix 7c).

Adverse Effects Dryness of skin; also pruritus, erythema, burning and irritation; hepatotoxicity, cholestasis; portal fibrosis; transient liver dysfunction; tautness of face.

Storage Store protected from light and moisture.

Nicotinic acid (Refer Page No. 343)

Pyridoxine* (Refer Page No. 621)

Pregnancy Category-A

Indications *Treatment of pyridoxine deficiency due to metabolic disorders; isoniazid neuropathy; sideroblastic anaemia.*

Availability **TABLETS** 10, 25, 40, 50 and 100 mg.

Dose ***Oral***

Adult- Deficiency states: 25 to 50 mg up to 3 times daily. Isoniazid neuropathy, prophylaxis: 10 mg daily. Isoniazid neuropathy, treatment: 50 mg, 3 times daily. Sideroblastic anaemia: 100 to 400 mg daily in divided doses.

Precautions Interactions (Appendix 6c), pregnancy (Appendix 7c).

Adverse Effects Generally well tolerated, but chronic administration of high doses may cause peripheral neuropathies; paresthesia; neurotoxicity; muscular weakness.

Riboflavin*

Pregnancy Category-A

Indications *Vitamin B_2 deficiency; arabinoflavinosis.*

Availability **TABLETS** 5 mg.

Dose ***Oral***

Adult and child- Treatment of vitamin B_2 deficiency: up to 30 mg daily in divided doses. Prophylaxis of vitamin B_2 deficiency: 1 to 2 mg daily.

Contraindications Cataract; hypersensitivity.

Precautions Large doses result in dark yellow discolouration of urine; pregnancy (Appendix 7c).

Adverse Effects Swelling of lips, face and tongue and difficulty in breathing.

Storage Store protected from light.

Sodium Fluoride

Indications *Prevention of dental caries.*

Availability **POWDER IN BULK**.

Dose ***As oral rinse***

Child- Prevention of dental caries: over 6 years of age 10 ml 0.05% solution daily or 10 ml 0.2% solution weekly.

Note: Fluoridated toothpastes are also a convenient source of fluoride for prophylaxis of dental caries.

Contraindications Not for areas where drinking water is fluoridated or where fluorine content is naturally high; neonates.

Precautions Kidney problems.

Adverse Effects In recommended doses toxicity unlikely; occasionally white flecks on teeth at recommended doses; rarely, yellowish-brown discolouration if recommended doses are exceeded; gum irritation.

Storage Store protected from moisture.

Thiamine*

Pregnancy Category-A

Indications *Prevention and treatment of vitamin B_1 deficiency, acute alcohol intoxication.*

Availability **TABLETS** 25, 50 and 100 mg.

Dose ***Oral***

Adult- Mild chronic thiamine deficiency: 10 to 25 mg daily.
Acute alcohol intoxication: 50-100 mg daily.
Wernicke-Korsakoff syndrome: 50-100 mg daily.

Precautions Parenteral administration (see notes above); lactation (Appendix 7b); pregnancy (Appendix 7c).

Adverse Effects Nausea; urticaria; gastrointestinal bleeding; oedema; pruritus; dizziness; anorexia.

Storage Store protected from light and moisture in a non-metallic container.

Vitamin A*

Pregnancy Category-X

Indications *Prevention and treatment of vitamin A deficiency; prevention of complications of measles.*

Availability **TABLETS** 5000 and 10,000 IU; **INJECTION** 50,000 IU/ml.

Dose ***Oral***

Adult- Prevention of vitamin A deficiency: 2,00,000 units every 6 months; pregnant woman, max. of 10,000 units daily or max. 25,000 units weekly; mothers, 200,000 units at delivery or within 6 weeks. Treatment of xerophthalmia; (except woman of child-bearing age) 2,00,000 units on diagnosis, repeated next day and then after 2 weeks; (woman of child-bearing age), 5000 to 10,000 units daily for at least 4 weeks or up to 25000 units weekly.

Child- Prevention of vitamin A deficiency: infant under 6 months, 50,000 units; 6 to 12 months, 100,000 units every 4 to 6 months, preferably at measles vaccination; over 1year, 200,000 units every 4 to 6 months. Treatment of xerophthalmia; infant under 6 months, 50,000 units on diagnosis, repeated next day and then after 2 weeks; 6 to 12 months, 1,00,000 units immediately on diagnosis, repeated next day and then after 2 weeks; over 1 year, same as adults.

Contraindications Hypervitaminosis.

Precautions Pregnancy (teratogenic; see notes above and Appendix 7c); lactation.

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; hair loss; redness of skin; anorexia; weight loss.

Storage Store protected from light and moisture.

Antianaemic 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 sulphate 300 mg (60 mg iron) and dried ferrous sulphate 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 Anaemia:

Megaloblastic anaemias result from a lack of either vitamin B_{12} (hydroxocobalamin) or folate 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 µg 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 12^{th} week 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.

Cyanocobalamin (Vitamin B_{12})*

Pregnancy Category-C

Indications — *Cyanocobalamin deficiency; peripheral neuropathy; diabetic neuropathy; medicine related or alcoholic neuropathy.*

Availability — **TABLETS** 50, 500 and 1500 µg; **CAPSULES** 50 µg; **LIQUID** 35 µg/5 ml; **INJECTION** vial 500 µg/30 ml.

Dose — ***Oral***

Adult- Vitamin-B_{12} deficiency of dietary origin: 50 to 150 µg daily between meals.

Child- 50 to 105 µg daily in 1 to 3 divided doses.

Intramuscular injection

Initially 1 mg repeated 10 times at intervals of 2 to 3 days, maintenance 1 mg every month.

Contraindications — Hypersensitivity, tobacco amblyopia.

Precautions — Cobalt hypersensitivity, pregnancy (Appendix 7c).

Adverse Effects — Asthenia; dyspepsia; pulmonary edema; shivering; bronchospasm.

Storage — Store protected from light in a single dose or multi dose container.

Erythropoietin

Pregnancy Category-C

Indications — *Anaemia of chronic renal failure, anaemia in patients with AIDs, anaemia associated with cancer chemotherapy, reduction of Allogeneic Blood Transfusion in Surgery Patients.*

Availability — **INJECTIONS** 1000, 2000, 3000, 4000, 5000, 6000, 10000, 20000 and 40000 IU/Vial

Dose — ***Parenteral***

Anaemia of chronic renal failure
Adult: As epoetin alfa: Initially, 50 U/kg subcutaneous/intravenous 3 times weekly for predialysis and haemodialysis patients and 50 U/kg twice weekly for peritoneal dialysis patients, dose may be increased according to response in steps of 25 U/kg 3 times weekly at 4 weekly intervals.
Child: As epoetin alfa: Initially, 50 U/kg 3 times weekly. Dose may be increased at 4 weekly intervals in increments of 25 U/kg 3 times weekly until a target haemoglobin concentration of 9.5-11 g/100 ml is reached. Usual maintenance dose: <10 kg: 225-450 U/kg/week; 10-30 kg: 180-450 U/kg/week and >30 kg: 90-300 U/kg/week.

Anaemia in zidovudine-treated HIV-infected patients
Adult: As epoetin alfa: Initially, 100 U/kg subcutaneous/intravenous thrice weekly for 8 weeks; increase every 4-8 week by 50-100 U/kg according to response. Max: 300 U/kg thrice weekly.

Subcutaneous
Anaemia related to non-myeloid malignant disease chemotherapy
Adult: As epoetin alfa or zeta: Initially, 150 U/kg 3 times weekly. Dose may be increased at 4-8 week intervals to 300 U/kg 3 times weekly. Stop treatment if response is still inadequate after 4 week of treatment using this higher dose.

Intravenous
Increase yield of autologous blood
Adult: As epoetin alfa or zeta: 600 U/kg over 2 minutes twice weekly for 3 week before surgery; in conjunction with iron, folate and B_{12} supplementation.

Contraindications

Hypersensitivity to mammalian cell products and human albumin, uncontrolled hypertension.

Precautions

Ischaemic heart diseases, chronic renal failure, hypertension, seizures, liver dysfunction, pregnancy (Appendix 7c) and lactation, interactions (Appendix 6c).

Adverse Effects

Nausea, vomiting, increased risk of hypertension, myalgia, arthralgia, rashes and urticaria, headache, confusion, generalized seizures, thrombosis specifically during dialysis, fever, diarrhoea, tissue swelling, flu-like syndrome, paraesthesia, constipation, nasal or chest congestion, immunogenicity leading to Pure Red Cell Aplasia.

Storage

Store in an air tight container at a temperature below - 20°C. Avoid repeated freezing and thawing.

Iron Salts*

Ferrous Gluconate, Ferrous Sulphate: Pregnancy Category A

Iron Sucrose, Sodium Ferric Gluconate: Pregnancy Category B

Iron Dextran: Pregnancy Category C

Indications

Iron-deficiency anaemia.

Availability

TABLETS (sugar coated, film coated) Ferrous sulphate 200 mg, Ferrous fumarate 200 mg, Ferrous gluconate 300 mg. (all equivalent to 65 mg elemental iron). In women, folic acid may also be given. **SYRUPS** also available. **CAPSULES** Iron sulfate 60-150 mg (20% Iron), Iron fumarate 200-300 mg (33% Iron). **INJECTIONS** Iron dextran 50 mg/ml, Iron sucrose 20, 50 and 100 mg/ml, Sodium ferric gluconate 12.5 mg/ml.

Dose

Oral

Adult- Iron-deficiency anaemia: elemental iron 100 to 200 mg daily in divided doses. Prevention of iron deficiency anaemia (in those at particular risk): for woman-elemental iron 60 mg daily.

Child- under 5 years: elemental iron 2 mg/kg (max. 30 mg) daily. Over 5 years: elemental iron 30 mg daily. Over 5 years: folic acid may also be given.

Parenteral

Total dose (ml) = 0.0442 (desired haemoglobin- obseved haemoglobin) x LBW + (0.26 x LBW)
[Note: LBW = Lean Body Weight (Kg)]
Total dose may be given in divided doses in a daily or twice weekly basis via IM inj. (into the upper quadrant of the buttock); may also be given intravenously by total-dose infusion or as divided inj. A-Z track technique (displacement of the skin laterally prior to injection) is recommended to avoid injection or leakage into subcutaneous tissue.

Contraindications

Haemosiderosis, haemochromatosis; any form of anaemia not caused by iron deficiency; evidence of iron overload; patients receiving repeated blood transfusions; parenteral iron therapy.

Precautions A test dose of 0.5 ml should be given & observe patien for at least 1 hour for signs of hypersensitivity, respiratory distress, tachycardia or back/chest pain; should not be administered for longer than 6 months; pregnancy (Appendix 7c); peptic ulcer; hypotension; regional enteritis, ulcerative colitis, intestinal strictures, diverticula; interactions (Appendix 6c, 6d).

Adverse Effects Nausea, vomiting, metallic taste; constipation, diarrhoea, dark stools, epigastric pain, gastrointestinal irritation; long-term or excessive administration may cause haemosiderosis; allergic reaction; back pain; staining of teeth.
Parenteral: Pain at injection site, sterile abscess.

Storage Store protected from light at temperature not exceeding 30°C.

Folic Acid*

Pregnancy Category-A

Indications *Treatment of folate-deficiency megaloblastic anaemia; prevention of neural tube defect in pregnancy.*

Availability **TABLETS** 1, 5 and 10 mg.

Dose ***Oral***

Adult- Treatment of folate-deficiency, megaloblastic anaemia: 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: 400 to 500 µg daily before conception and during the first twelve weeks of pregnancy.

Prevention of recurrence of neural tube defect: 5 mg daily (reduced to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until twelfth week of pregnancy.

Contraindications Should never be given without vitamin B_{12} in undiagnosed megaloblastic anaemia or other vitamin B_{12} 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; pernicious anaemia; folate dependent tumor; interactions (Appendix 6c); pregnancy (Appendix 7c).

Adverse Effects Neuropathy; bronchospasm; skin eruption; anorexia; skin rash; status epilepticus.

Storage Store protected from light.

Hydroxocobalamin

Pregnancy Category-C

Indications *Megaloblastic anaemia due to vitamin B_{12} deficiency, congenital intrinsic factor disease.*

Availability **INJECTION** 1 ml (1 mg/ml).

Dose ***Intramuscular injection***

Adult and Child- Megaloblastic anaemia without neurological involvement: initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months.

Megaloblastic anaemia with neurological involvement: initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months.

Prophylaxis of macrocytic anaemias: 1 mg every 2 to 3 months.

Tobacco amblyopia and Leber optic atrophy: 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1 to 3 months.

Contraindications Anaphylactic reaction.

Precautions Except in emergencies, should not be given before diagnosis confirmed; monitor serum potassium levels-arrhythmias secondary to hypokalaemia in early therapy; pregnancy (Appendix 7c).

Adverse Effects Itching, exanthema, fever, chills, hot flushes, nausea, dizziness; rarely, acneiform and bullous eruptions, anaphylaxis; hypersensitivity; headache; diarrhoea.

Storage Store protected from light.

Iron Dextran*

Pregnancy Category-C

Schedule H

Indications *Iron deficiency anaemia, prevention of iron deficiency before, during or after pregnancy, to make up iron deficiency after pregnancy and during lactation.*

Availability **INJECTION** (iron as iron dextran) 1.5 ml ampoule (50 mg/ml).

Dose

Deep intramuscular injection into the gluteal muscle or slow intravenous injection or intravenous infusion.

Adult- Calculated according to body-weight and iron deficit. While deciding on parenteral therapy, oral therapy should be stopped at least 24 h before. Urine may darken on starting.

Child- Under 14 years: not recommended.

Contraindications

History of allergic disorders including asthma and eczema; infection; active rheumatoid arthritis; liver disease.

Precautions

Oral iron not to be given until 5 days after last injection; hepatic impairment; renal impairment; pregnancy (Appendix 7c); interactions (Appendix 6d).

Anaphylactic reactions can occur with parenteral iron and a test dose is recommended before each dose; the patient should be carefully observed for 60 min after the first test dose and for 15 min after subsequent test doses (subsequent test doses not necessary for intramuscular administration). Facilities for cardiopulmonary resuscitation must be at hand; risk of allergic reactions increased in immune or inflammatory conditions.

Adverse Effects

Less commonly nausea, vomiting, abdominal pain, flushing, dyspnoea, anaphylactic reactions (see Anaphylaxis above), numbness, cramps, blurred vision, pruritus and rash; rarely, diarrhoea, chest pain, hypotension, angioedema, arrhythmias, tachycardia; dizziness, restlessness, fatigue; seizures, tremor, impaired consciousness, myalgia, arthralgia and sweating; injection-site rea ctions also reported, thrombophlebitis; peripheral vascular flushing; taste disturbances; syncope.

Pyridoxine* (Refer Page No. 610)

Pregnancy Category-A

Indications

Isoniazid, hydralazine and cycloserine induced-neurological disturbances; pyridoxine responsive anaemia and haemocysteinurea; morning sickness and hyperemesis gravidarum; convulsions in infants and children; mental symptoms in women on oral contraceptives.

Availability

TABLETS 10, 25, 40 and 50 mg and 100 mg (sustained release); **INJECTION** 1 ml (50 mg/ml).

Dose

Oral

Adult-Deficiency states: 25 to 50 mg up to 3 times daily.

Isoniazid neuropathy (prophylaxis: 10 mg daily.

Isoniazid neuropathy (treatment): 50 mg 3 times daily.

Sideroblastic anaemia: 100 to 400 mg daily in divided doses.

Precautions

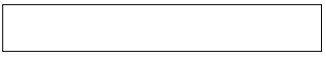
Interactions (Appendix 6c); pregnancy (Appendix 7c); long term administration of high dose may cause severe peripheral neuropathies.

Adverse Effects

Sensory neuropathy reported with high doses given for extended periods, numbness; neurotoxicity; hyperesthesia; muscle weakness.

Storage

Store protected from light and moisture.



Appendices

Appendix 6a:
Drug-Alcohol Interactions

Mixing alcohol with medications can cause a variety of symptoms like nausea, vomiting, headache, drowsiness, fainting, or loss of coordination. By virtue of its effects on the CNS consumption of alcohol, even in small quantities, puts the patient at a high risk. There are medicines which should never be taken with alcohol (Table 1). However, there are many other medicines which should be used with high level of caution while the patient is on alcohol (Table 2).

Table 1: Drugs not to be used with alcohol

Acetylsalicylic Acid	Losartan
Alprazolam	Lovastatin
Amitriptyline	Lovastatin+ Niacin
Atorvastatin	Meperidine
Benazepril	Metronidazole
Butalbital + Codeine	Naproxen
Carisoprodol	Nicotinic acid
Cefoperazone	Nitrazepam
Chlordiazepoxide	Nitrofurantoin
Clomipramine	Nitroglycerin
Clonazepam	Paracetamol
Clonidine	Paroxetine
Cyclobenzaprine	Phenobarbital
Desipramine	Phenytoin
Diazepam	Pravastatin
Diphenhydramine	Pravastatin + Acetylsalicylic acid
Doxazosin	Prazosin
Doxylamine	Propoxyphene
Enalapril	Quinapril
Eszopiclone	Ramipril
Fluoxetine	Rosuvastatin
Griseofulvin	Simvastatin
Herbal Preparations	Simvastatin + Ezetimibe
Hydrochlorothiazide	Temazepam
Ibuprofen	Terazosin
Isoniazid	Tinidazole
Isosorbide	Vitamin D
Ketoconazole	Warfarin
Leflunomide	Zolpidem
Lorazepam	

Table 2: Drugs to be avoided with alcohol

Abacavir Amobarabital Atenolol Atropine Bromocriptine Brompheniramine Cetirizine Chlorpheniramine Chlorpromazine Cimetidine Dextromethorphan Diclofenac Dimenhydrinate Diphenhydramine Doxycycline Fexofenadine Fluphenazine Furazolidone Glyburide Guaifenesin + Codeine Haloperidol Imipramine Insulin Loratadine	Metformin Methadone Methotrexate Metoclopramide Midazolam Morphine Nizatidine Oxytocin Pentazocine Prazosin Procarbazine Prochlorperazine Promethazine Propranolol Ranitidine Sodium Valproate Tamsulosin Thiopental Tolbutamide Trifluoperazine Trihexyphenidyl

Appendix 6b: Drug–Contraceptive Interactions

CONTRACEPTIVES, ORAL

Acetazolamide	Antagonism of diuretic effect
Amiloride	Antagonism of diuretic effect
Amitriptyline	Antagonism of antidepressant effect but adverse effects increased due to increased plasma concentration of amitriptyline
Amoxycillin	Reduced contraceptive effect of estrogen-containing preparations
Ampicillin	Reduced contraceptive effect of estrogen-containing preparations
Atenolol	Antagonism of hypotensive effect
Carbamazepine	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception); reduced contraceptive effect (does not apply to injectable norethisterone enantate for contraception)
Ceftazidime	Reduced contraceptive effect of estrogen-containing preparations
Ceftriaxone	Reduced contraceptive effect of estrogen-containing preparations
Cefuroxime	Reduced effect of contraceptives
Corticosteroids	Oral contraceptives increase plasma concentration of corticosteroids
Clomipramine	Antagonism of antidepressant effect but adverse effects increased due to increased plasma concentration of clomipramine
Cyclosporine	Inhibition of cyclosporine metabolism (increased plasma–cyclosporine concentration)
Doxycycline	Reduced contraceptive effect of estrogen-containing preparations
Efavirenz	Efficacy of oral contraceptives reduced
Enalapril	Antagonism of hypotensive effect
Fluconazole	Anecdotal reports of contraceptive failure

Fosphenytoin	Reduced contraceptive effect
Furosemide	Antagonism of diuretic effect
Glibenclamide	Antagonism of hypoglycaemic effect
Glimepiride	Reduced hypoglycaemic action
Glucagon	Antagonism of hypotensive effect
Glyceryl trinitrate	Antagonism of hypotensive effect
Griseofulvin	Reduced contraceptive effect of levonorgestrel, accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception); does not apply to injectable norethisterone enantate for contraception
Hydralazine	Antagonism of hypotensive effect
Hydrochlorothiazide	Antagonism of diuretic effect
Insulins	Antagonism of hypoglycaemic effect
Isosorbide dinitrate	Antagonism of hypotensive effect
Metformin	Antagonism of hypoglycaemic effect
Methyldopa	Antagonism of hypotensive effect
Nelfinavir	Accelerated metabolism of levonorgestrel, medroxyprogesterone and norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogestrone acetate for contraception
Nevirapine	Accelerated metabolism of levonorgestrel, medroxyprogesterone and norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogestrone acetate for contraception
Nifedipine	Antagonism of hypotensive effect
Phenobarbital	Metabolism accelerated (reduced contraceptive effect); does not apply to injectable medroxyprogestrone acetate for contraception; does not apply to injectable norethisterone enantate for contraception
Phenytoin	Accelerated metabolism of levonorgestrel, norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogestrone acetate for contraception; does not apply to injectable norethisterone enantate for contraception

Propranolol	Antagonism of hypotensive effect
Rifampicin	Accelerated metabolism of levonorgestrol and medroxyprogesterone (reduced contraceptive effect); does not apply to injectable medroxyprogestrone acetate for contraception; does not apply to injectable norethisterone enantate for contraception
Ritonavir	Accelerated metabolism of levonorgestrol and norethisterone (reduced contraceptive effect); does not apply to injectable medroxyprogestrone acetate for contraception; does not apply to injectable norethisterone enantate for contraception
Sodium nitroprusside	Antagonism of hypotensive effect
Spironolactone	Antagonism of diuretic effect
Topiramate	Failure of contraceptive effect
Theophylline	Delayed excretion of theophylline; increased plasma concentration
Verapamil	Antagonism of hypotensive effect
Warfarin	Antagonism of anticoagulant effect

Appendix 6c: Drug–Drug Interactions

Two or more drugs administred at the same time may interact with each other. The interactions may be potentiation or antagonism of one drug by another or occasionally some other effect. Drug interactions may be of pharmacokinetic or pharmacodynamic type. The pharmacokinetic interactions can be because of absorption mechanism, competition of two drugs at the protein binding sites, metabolizing enzyme system or excretion. When two or more drugs are concomitantly administered there is always a possibility of pharmacokinetic or pharmacodynamic interaction. The pharmacodynamic interactions can be at the receptor level for competition at same drug target (enzyme/receptor) acting synergistically or antagonizing the effect of each other. The drugs which have narrow therapeutic window have greater potential to cause unexpected adverse effect when their pharmacokinetics or pharmacodynamics is altered. In such situation, the following precautions are advisable:

1. Concomitant administration of drugs should possibly be avoided.
2. When unavoidable, care should be taken and TDM is recommended.
3. When TDM is not possible logistically, clinical symptomatology be done.
4. Careful dose titration (upward/downward) be done to get optimum dose modification.

The following drug categories are considered as drugs of narrow therapeutic window:

Antiepileptics, anticoagulants, anticancers, xanthenes, antidepressants, antiarrhythmics etc.

Some representative clinically relevant drug–drug interactions are listed below:

ABCIXIMAB	
Anticoagulants	Increased risk of bleeding
Antiplatelet agents	Increased risk of bleeding
ACETAZOLAMIDE	
Carbamazepine	Increased risk of hyponatraemia; acetazolamide increases plasma–carbamazepine concentration

Digoxin	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Furosemide	Increased risk of hypokalaemia
Nifedipine	Enhanced hypotensive effect
Phenytoin	Increased risk of osteomalacia
ACETYLSALICYLIC ACID	
Corticosteroids	Increased risk of gastrointestinal bleeding and ulceration; corticosteroids reduce plasma–salicylate concentration
Heparin	Enhanced anticoagulant effect
Methotrexate	Reduced excretion of methotrexate (increased toxicity)
Warfarin	Increased risk of bleeding due to antiplatelet effect
ALENDRONATE	
Calcium supplements	Reduced absorption of alendronate
Antacids	Reduced absorption of alendronate
ALLOPURINOL	
Azathioprine	Effects of azathioprine enhanced with increased toxicity; reduce dose when given with allopurinol
Mercaptopurine	Effects of 6-mercaptopurine enhanced with increased toxicity; reduce dose when given with allopurinol
ALTEPLASE	
Prostacyclin, nitrates	Increased plasma–alteplase clearance
Abciximab	Additive effect
Nitroglycerin	Decreased thrombolytic effect of alteplase
Warfarin, Antiplatelet agents	Increased risk of bleeding
NSAIDs	Increased risk of GI bleeding

AMILORIDE	
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Cyclosporine	Increased risk of hyperkalaemia
Enalapril	Enhanced hypotensive effect; risk of severe hyperkalaemia
AMINOPHYLLINE	
Febuxostat	Increased effect of aminophylline.
Rifamycin	Decreased effect of aminophylline.
AMITRIPTYLINE	
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Carbamazepine	Antagonism of anticonvulsant effect
Haloperidol	Increased plasma–amitriptyline concentration; increased risk of ventricular arrhythmias
Phenobarbital	Antagonism of anticonvulsant effect
Phenytoin	Antagonism of anticonvulsant effect
Valproic acid	Antagonism of anticonvulsant effect
AMOXYCILLIN	
Methotrexate	Reduced excretion of methotrexate; increased risk of toxicity
AMOXYCILLIN + CLAVULANIC ACID	
Probenecid	Increased concentrations of amoxycillin in serum and bile
Allopurinol	Occurrence of allergic cutaneous reactions
Digoxin	Increased absorption
Warfarin	Increased incidence of bleeding
AMPHOTERICIN B	
Corticosteroids	Increased risk of hypokalaemia

Cyclosporine	Increased risk of nephrotoxicity
Digoxin	Increased digoxin toxicity if hypokalaemia occurs
Tacrolimus	Synergistic effect of amphotercin

AMPICILLIN

Methotrexate	Reduced excretion of methotrexate; increased risk of toxicity
Warfarin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin

ANTACIDS (ALUMINIUM HYDROXIDE; MAGNESIUM HYDROXIDE)

Note: Antacids should preferably not be taken at the same time as other drugs since they may impair absorption

Ciprofloxacin	Reduced absorption of ciprofloxacin
Digoxin	Reduced absorption of digoxin
Isoniazid	Reduced absorption of isoniazid
Phenytoin	Reduced absorption of phenytoin
Rifampicin	Reduced absorption of rifampicin

ARTEMETHER + LUMEFANTRINE

Amitriptyline	Increased risk of ventricular arrhythmias
Azithromycin	Avoid concomitant use
Chloroquine	Increased risk of ventricular arrhythmias
Ciprofloxacin	Avoid concomitant use
Fluconazole	Avoid concomitant use
Furosemide	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Mefloquine	Increased risk of ventricular arrhythmias
Ofloxacin	Avoid concomitant use
Pyrimethamine	Avoid concomitant use

Quinine	Increased risk of ventricular arrhythmias
Sulfadoxine + Pyrimethamine	Avoid concomitant use
ATENOLOL	
Glibenclamide	Masking of warning signs of hypoglycaemia such as tremor
Insulins	Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Lidocaine	Increased risk of myocardial depression
Nifedipine	Severe hypotension and heart failure occasionally
Verapamil	Asystole, severe hypotension and heart failure
ATORVASTATIN	
Ketoconazole	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Itraconazole	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Ritonavir	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Erythromycin	Increased plasma concentration of atorvastatin and risk of myotoxicity in frequent
Fibrates	Increased risk of rhabdomyolysis
AZATHIOPRINE	
Allopurinol	Effects of azathioprine enhanced
Phenytoin	Reduced absorption of phenytoin
Rifampicin	Transplants rejected
Sulfamethoxazole + Trimethoprim	Increased risk of haematological toxicity
Vaccines, Live	Avoid use of live vaccines with azathioprine (impairment of immune response)
Warfarin	Reduced effect of anticoagulant

AZITHROMYCIN	
Cyclosporine	Plasma concentration of cyclosporine increased
Digoxin	Effect of digoxin enhanced
Warfarin	Enhanced anticoagulant effect of warfarin
BACLOFEN	
Tricyclic antidepressents	Risk of muscle weakness
MAO inhibitors	Depression of brain function as well as low blood pressure
Antidiabetic drugs	Increased blood sugar level
BENZATHINE BENZYLPENICILLIN	
Aminoglycosides	Reduced effect of aminoglycosides in patient with renal impairment
Methotrexate	Reduced excretion of methotrexate
BLEOMYCIN	
Vaccines, Live	Avoid use of live vaccines with bleomycin (impairment of immune response)
Vinblastine	Increased risk of cardiovascular toxicity
BROMOCRIPTINE	
Ergot derivatives	Additive dopamine agonistic activity
BUDESONIDE	
Ketoconazole	Plasma concentration of orally administered budesonide increased
Itraconazole	Metabolism of budesonide inhibited
Clarithromycin	Metabolism of budesonide inhibited
Erythromycin	Metabolism of budesonide inhibited
BUPIVACAINE	
Lidocaine	Increased myocardial depression
Procainamide	Increased myocardial depression
Quinidine	Increased myocardial depression

BUSULPHAN	
Itraconazole	Increased level of busulphan
Metronidazole	Increased level of busulphan
Nalidixic acid	Risk of gastrointestinal toxicity
Thioguanine	Risk of portal hypertension and espohageal varices
CALCIUM CARBONATE + VITAMIN D_3	
Quinolones	Risk of decreased absorption into the body
Tetracycline	Risk of decreased absorption into the body
Mycophenolate mofetil	Decreased effectiveness of mycophenolate mofetil
CALCIUM SALTS	
Digoxin	Large intravenous doses of calcium can precipitate arrhythmias
Tetracyclines	Reduced absorption of tetracyclines
CAPREOMYCIN	
BCG vaccine	May make the vaccine ineffective
Neuromuscular blocking agents	Increase in neuromuscular blocking effects
Typhoid vaccine	May make the vaccine ineffective
CARBAMAZEPINE	
Acetazolamide	Increased risk of hyponatraemia; acetazolamide increases plasma–carbamazepine concentration
Amitriptyline	Antagonism (convulsive threshold lowered); accelerated metabolism of amitriptyline; reduced plasma concentration; reduced effect antidepressant
Chloroquine	Convulsive threshold occasionally lowered
Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Corticosteroids	Accelerated metabolism of corticosteroids

Cyclosporine	Accelerated metabolism (reduced plasma–cyclosporine concentration)
Diltiazem	Increased carbamazepine level
Erythromycin	Increased plasma–carbamazepine concentration
Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Haloperidol	Antagonism of anticonvulsant effect
Isoniazid	Increased plasma–carbamazepine concentration (also isoniazid hepatotoxicity increased)
Lopinavir	Reduced plasma-lopinavir concentration
Progestins	Accelerated metabolism of progestins
Sulfamethoxazole + Trimethoprim	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine often lowered
Phenytoin	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered
Ritonavir	Plasma concentration increased by ritonavir
Valproic acid	Plasma concentration of valproic acid often lowered; plasma concentration of active metabolite of carbamazepine often raised
Verapamil	Enhanced effect of carbamazepine
Warfarin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
CEFAZOLIN	
Oral anticoagulants	Increased hypoprothrombinemic effect of anticoagulant.
CEFIXIME	
Carbamazepine	Elevated carbamazepine levels

Anticoagulants	Increased prothrombin time
CEFTAZIDIME	
Furosemide	Nephrotoxicity of ceftazidime increased
Warfarin	Enhanced anticoagulant effect
CEFTRIAXONE	
Warfarin	Enhanced anticoagulant effect
CHLORAMPHENICOL	
Cyclosporine	Plasma concentration of cyclosporine increased
Iron	Avoid as can cause bone marrow depression which appears treatment of anaemia
Phenobarbital	Metabolism of chloramphenicol accelerated (reduced chloramphenicol concentration)
Phenytoin	Plasma–phenytoin concentration increased (risk of toxicity)
Vitamin B_{12}	Avoid concomitant use, can cause bone marrow depression
CHLOROQUINE	
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Carbamazepine	Convulsive threshold occasionally lowered
Cyclosporine	Increased plasma–cyclosporine concentration (increased risk of toxicity)
Digoxin	Plasma–digoxin concentration increased
Mefloquine	Increased risk of convulsions
Phenytoin	Convulsive threshold occasionally lowered
Valproic acid	Convulsive threshold occasionally lowered
CHLORPROMAZINE	
Amitriptyline	Increased antimuscarinic adverse effects; increased plasma-amitriptyline concentration; increased risk of ventricular arrhythmias

Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Clomipramine	Increased antimuscarinic adverse effects; increased plasma-clomipramine concentration; increased risk of ventricular arrhythmias
Ether, Anaesthetic	Enhanced hypotensive effect
Halothane	Enhanced hypotensive effect
Ketamine	Enhanced hypotensive effect
Nitrous oxide	Enhanced hypotensive effect
Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Procainamide	Increased risk of ventricular arrhythmias
Propranolol	Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect
Quinidine	Increased risk of ventricular arrhythmias
Ritonavir	Plasma concentration increased by ritonavir
Thiopental	Enhanced hypotensive effect
Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
CINNARIZINE	
CNS depressants (alcohol, barbiturates, hypnotics, narcotic analgesics, tricyclic antidepressants, sedatives and tranquillizers)	Additive sedation
Zolpidem	Additive toxicity
CIPROFLOXACIN	
Artemether + Lumefantrine	Avoid concomitant use
Cyclosporine	Increased risk of nephrotoxicity
Glibenclamide	Enhanced effect of glibenclamide

Ibuprofen	Increased risk of convulsions
Warfarin	Enhanced anticoagulant effect
CISPLATIN	
Aminoglycoside antibiotics	Increased risk of nephrotoxicity and ototoxicity
Furosemide	Increased risk of nephrotoxicity and ototoxicity
Hydrochlorothiazide	Increased risk of nephrotoxicity and ototoxicity
Vancomycin	Increased risk of nephrotoxicity and ototoxicity
CLARITHROMYCIN	
Oral anticoagulants	Increased anticoagulant effect.
Carbamazepine	Increased serum concentration of carbamazepine.
Digoxin	Increased concentration of digoxin.
Lovastatin	Avoid concomitant use
Sildenafil	Dose reduction of sildenafil may be required.
Simvastatin	Avoid concomitant use
Sirolimus	Elevation in serum sirolimus level
Tacrolimus	Elevation in serum sirolimus level
Tadalafil	Dose reduction of tadalafil may be required.
CLINDAMYCIN	
Erythromycin	Antagonist activity
Pancuronium	Neuromuscular blockade exaggerated
Kaoli-pectin	Reduced absorption rate
Gentamycin	Synergistic effect
CLOBAZAM	
Cimetidine	Increased effect of clobazam
Barbiturates	Decreased serum level of clobazam
CLONAZEPAM	

Carbamazepine	Decreased level of carbamazepine
Ketoconazole	Inhibition of metabolism of clonazepam
CLOPIDOGREL	
Omeprazole	Plasma concentration of active metabolite of clopidogrel is decreased
NSAIDs	Increased risk of gastrointestinal bleeding
CLONIDINE	
Beta blockers	Sinus bradycardia, monitor heart rate
Clomipramine	Risk of hypertensive crisis
CODEINE	
Diazepam	Enhanced sedative effect
Ritonavir	Ritonavir increases plasma concentration of codeine
CORTICOSTEROIDS	
Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma-salicylate concentration
Amphotericin B	Increased risk of hypokalaemia
Atenolol	Antagonism of hypotensive effect
Carbamazepine	Accelerated metabolism of hydrocortisone (reduced effect)
Digoxin	Increased risk of hypokalaemia
Enalapril	Antagonism of hypotensive effect
Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide	Antagonism of hypoglycaemic effect
Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
Insulins	Antagonism of hypoglycaemic effect
Levonorgestrel	Levonorgestrel increases plasma concentration of corticosteroids

Methotrexate	Increased risk of haematological toxicity
Nifedipine	Antagonism of hypotensive effect
Phenobarbital	Metabolism of hydrocortisone accelerated (reduced effect)
Phenytoin	Metabolism of hydrocortisone accelerated (reduced effect)
Rifampicin	Accelerated metabolism of corticosteroids (reduced effect)
Salbutamol	Increased risk of hypokalaemia if high doses of corticosteroids given with high doses of salbutamol
Warfarin	Anticoagulant effect altered
CYCLOPHOSPHAMIDE	
Vaccines, Live	Avoid use of live vaccines with cyclophosphamide (impairment of immune response)
CYCLOSPORINE	
Amphotericin B	Increased risk of nephrotoxicity
Ciprofloxacin	Increased risk of nephrotoxicity
Digoxin	Reduced clearance of digoxin (risk of toxicity)
Enalapril	Increased risk of hyperkalaemia
Erythromycin	Increased plasma-cyclosporine concentration
Methotrexate	Increased toxicity
Metoclopramide	Plasma-cyclosporine concentration increased
Ofloxacin	Increased risk of nephrotoxicity
Phenobarbital	Metabolism of cyclosporine accelerated
Phenytoin	Accelerated metabolism
Rifampicin	Accelerated metabolism (reduced plasma-cyclosporine concentration)
Ritonavir	Plasma concentration increased by ritonavir
Rosuvastatin	Marked rise in serum rosuvastatin level

Sulfonamides and Trimethoprim	Increased toxicity
Vaccines, Live	Avoid use of live vaccines with cyclosporine
Vancomycin	Increased risk of nephrotoxicity
DANAZOL	
Anticoagulants (warfarin)	Danazol inhibits metabolism of coumarins
Cyclosporine	Danazol inhibits metabolism of cyclosporine
Lovastatin	Increased risk of myopathy
Simvastatin	Increased risk of myopathy
Tacrolimus	Danazol increases plasma concentration of tacrolimus
DAPSONE	
Rifampicin	Reduced plasma-dapsone concentration
Sulfamethoxazole + Trimethoprim	Plasma concentration of both dapsone and trimethoprim increased with concomitant use
DESFERRIOXAMINE MESYLATE	
Ascorbic acid	May worsen iron toxicity
DEXAMETHASONE	
Acetazolamide	Increased risk of hypokalaemia; antagonism of diuretic effect
Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma-salicylate concentration
Albendazole	Plasma-albendazole concentration increased
Amiloride	Antagonism of diuretic effect
Amphotericin B	Increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions)
Atenolol	Antagonism of hypotensive effect
Carbamazepine	Accelerated metabolism of dexamethasone (reduced effect)
Digoxin	Increased risk of hypokalaemia

Enalapril	Antagonism of hypotensive effect
Ephedrine	Metabolism of dexamethasone accelerated
Erythromycin	Erythromycin inhibits metabolism of dexamethasone
Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
Glibenclamide	Antagonism of hypoglycaemic effect
Glyceryl trinitrate	Antagonism of hypotensive effect
Hydralazine	Antagonism of hypotensive effect
Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
Indinavir	Reduced plasma-indinavir concentration
Insulins	Antagonism of hypoglycaemic effect
Isosorbide dinitrate	Antagonism of hypotensive effect
Levonorgestrel	Levonorgestrel increases plasma concentration of dexamethasone
Lopinavir	Reduced plasma-lopinavir concentration
Medroxyprogesterone	Medroxyprogesterone increases plasma concentration of dexamethasone
Metformin	Antagonism of hypoglycaemic effect
Methotrexate	Increased risk of haematological toxicity
Methyldopa	Antagonism of hypotensive effect
Nifedipine	Antagonism of hypotensive effect
Norethisterone	Norethisterone increases plasma concentration of dexamethasone

Phenobarbital	Metabolism of dexamethasone accelerated (reduced effect)
Phenytoin	Metabolism of dexamethasone accelerated (reduced effect)
Praziquantel	Plasma-praziquantel concentration reduced
Propranolol	Antagonism of hypotensive effect
Rifampicin	Accelerated metabolism of dexamethasone (reduced effect)
Ritonavir	Increased plasma concentration by ritonavir
Salbutamol	Increased risk of hypokalaemia if high doses of dexamethasone given with high doses of salbutamol
Saquinavir	Reduced plasma-saquinavir concentration
Sodium nitroprusside	Antagonism of hypotensive effect
Spironolactone	Antagonism of diuretic effect
Theophylline	Increased risk of hypokalaemia
Vaccines, Live	High doses of dexamethasone impair immune response; avoid use of live vaccines
Verapamil	Antagonism of hypotensive effect
Warfarin	Anticoagulant effect altered
DEXTRAN 40	
Abciximab	Additive effect
DEXTROMETHORPHAN	
MAO Inhibitors	Risk of hypotension, hyperpyrexia, sedation etc.
Sibutramine	Risk of serotonin syndrome
DIAZEPAM	
Atenolol	Enhanced hypotensive effect
Enalapril	Enhanced hypotensive effect
Furosemide	Enhanced hypotensive effect

Glyceryl trinitrate	Enhanced hypotensive effect
Ritonavir	Plasma concentration increased by ritonavir
DICLOFENAC	
Cyclosporine	Decreased renal function
Methotrexate	Increased levels of methotrexate.
DICYCLOMINE	
Antidepressants	Increased risk of antimuscarinic side effects
Antipsychotics	Antimuscarinics reduce effects of haloperidol; increased risk of antimuscarinic side effects when antimuscarinics given with clozapine; antimuscarinics reduce plasma concentration of phenothiazines, but risk of antimuscarinic side effects increased
DIDANOSINE	
Divalproex	Risk of additive toxicity
Ganciclovir	Increased didanosine concentration
Metronidazole	Risk of additive toxicity
Pentamidine	Risk of additive toxicity
Stavudine	Risk of additive toxicity
Vinblastine	Risk of additive toxicity
DIGOXIN	
Acetazolamide	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Amphotericin B	Increased digoxin toxicity if hypokalaemia occurs
Atenolol	Increased AV block and bradycardia
Corticosteroids	Increased risk of hypokalamia
Cyclosporine	Reduced clearance of digoxin (risk of toxicity)
Furosemide	Cardiac toxicity of digoxin increased if hypokalaemia occurs

Hydrochlorothiazide	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Nifedipine	Increased plasma concentration of digoxin
Timolol	Increased AV block and bradycardia
Verapamil	Increased plasma concentration of digoxin; increased AV block and bradycardia
DIHYDROERGOTAMINE	
Amiodarone	Increased cardiac depressant effects
Azoles antifungal	Increased level of alkoloid
Buspirone	Increased serum level of buspirone
Macrolide antibiotics	Increased plasma level of unchanged alkaloid and peripheral vasoconstriction
Protease inhibitors	Elevated levels of ergot alkaloids
Sumatriptan	Additive effect with dihydroergotamine
DILTIAZEM	
Carbamazepine	Increased serum level of carbamazepine
Rifampin	Decreased diltiazem plasma concentration
DOBUTAMINE	
Beta-blockers	Risk of peripheral resistance
DOMPERIDONE	
Amiodarone	Additive toxicity with amiodarone.
DOPAMINE	
Ergometrine	Increased risk of ergotism
Haloperidol	Antagonism of pressor action
DOXORUBICIN	
Cyclosporine	Increased risk of neurotoxicity
Cyclophosphamide	Chances of exacerbation of cyclophosphamide-induced hemorrhagic cystitis

Digoxin	Decreased digoxin levels
Paclitaxel	Increased risk of cardiotoxicity
Progesterone	Increased risk of doxorubicin-induced neutropenia
Quinidine	Increases the levels of doxorubicin
Stavudine	Decreased level and effectiveness of stavudine
Vaccines, Live	Avoid use of live vaccines with doxorubicin
Zidovudine	Decreased effect of zidovudine.
DOXYCYCLINE	
Cyclosporine	Increased plasma-cyclosporine concentration
Ergotamine	Increased risk of ergotism
Warfarin	Anticoagulant effect enhanced
EFAVIRENZ	
Ergot derivatives	Increased chance of ergotism
Itraconazole	Decreased plasma level of itraconazole
Lopinavir	Plasma concentration of lopinavir reduced
Ritonavir	Increased risk of toxicity
ENALAPRIL	
Acetylsalicylic acid	Antagonism of hypotensive effect; increased risk of renal impairment
Antacids	Absorption of enalapril reduced
Cyclosporine	Increased risk of hyperkalaemia
Glibenclamide	Hypoglycaemic effect enhanced
Heparin	Increased risk of hyperkalaemia
Lithium	Increased plasma-lithium concentration
Spironolactone	Enhanced hypotensive effect, risk of severe hyperkalaemia
EPINEPHRINE (ADRENALINE)	
Halothane	Risk of arrhythmias

ERYTHROMYCIN	
Artemether + Lumefantrine	Avoid concomitant use
Carbamazepine	Increased plasma-carbamazepine concentration
Corticosteroids	Inhibits metabolism of corticosteroids
Cyclosporine	Increased plasma-cyclosporine concentration
Digoxin	Enhanced effect of digoxin
Warfarin	Enhanced anticoagulant effect
ERYTHROPOIETIN	
Haematinics	Enhanced efficiency of erythropoietin.
ESCITALOPRAM	
Carbamazepine	Carbamazepine toxicity may be precipitated
ESMOLOL	
Verapamil	Chances of cardiac arrest
ETHINYL ESTRADIOL	
Hydantoin	Decreased effect of estrogen
ETOPOSIDE	
Vaccines, Live	Avoid use of live vaccines with etoposide
EZETIMIBE	
Bile Acid Sequestrants	Decreased levels and clinical effectiveness of ezetimibe
Fibrates	Elevated levels of ezetimibe leading to toxicity.
Cyclosporine	Increased ezetimibe levels in patients with severe renal insufficiency.
FACTOR IX	
Acetylsalicylic acid	Risk of bleeding
FAMOTIDINE	
Antacids	Reduced absorption of famotidine
Ketoconazole, itraconazole	Reduced absorption of ketoconazole and itraconazole

Ethanol	Gastric mucosal irritation may occur.
FENOFIBRATE	
Anticoagulants	Increased effect of anticoagulants
Statins	Increased risk of kidney and muscle problems
Cyclosporine	Increased risk of nephrotoxicity
FERROUS SALTS	
Ciprofloxacin	Absorption of ciprofloxacin reduced by oral ferrous salts
Doxycycline	Reduced absorption of oral ferrous salts by doxycycline; reduced absorption of doxycycline by oral ferrous salts
Methyldopa	Reduced hypotensive effect of methyldopa
FEXOFENADINE	
Antacids	Decreased absorption of fexofenadine
Erythromycin	Increased plasma concentration of fexofenadine
Ketoconazole	Increased plasma concentration of fexofenadine
FLUCONAZOLE	
Artemether + Lumefantrine	Avoid concomitant use
Cyclosporine	Metabolism of cyclosporine inhibited
Glibenclamide	Plasma concentration of glibenclamide increased
Rifampicin	Accelerated metabolism of fluconazole
Warfarin	Enhanced anticoagulant effect
Zidovudine	Increased plasma concentration of zidovudine (increased risk of toxicity)
FLUCYTOSINE	
Amphotericin B	Renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity increased)

5-FLUOROURACIL	
Metronidazole	Metabolism of 5-fluorouracil inhibited
Phenytoin	Reduced absorption of phenytoin
Warfarin	Anticoagulant effect enhanced
FLUOXETINE	
Benzodiazepines	Increased level of benzodiazepines
Clozapine	Increased levels of clozapine
Selected MAO inhibitors	Risk of serotonin syndrome
FLUPHENAZINE	
Amitriptyline	Increased antimuscarinic adverse effects; increased plasma-amitriptyline concentration; increased risk of ventricular arrhythmias
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias
Atenolol	Enhanced hypotensive effect
Carbamazepine	Antagonism of anticonvulsant effect
Enalapril	Enhanced hypotensive effect
Lithium	Increased risk of extrapyramidal effects and neurotoxicity
Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Metoclopramide	Increased risk of extrapyramidal effects
Nifedipine	Enhanced hypotensive effect
Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)

FOLIC ACID AND FOLINIC ACID	
Phenobarbital	Plasma concentration of phenobarbital reduced
Phenytoin	Plasma-phenytoin concentration reduced
FORMOTEROL + FLUTICASONE PROPIONATE	
Ritonavir	Systemic corticosteroid effects including cushing syndrome and adrenal suppression
Ketoconazole	Increased plasma fluticasone propionate concentrations.
MAO inhibitors	Increased risk of cardiovascular adverse effects.
FOSPHENYTOIN	
Albendazole	Efficacy is impaired by phenytoin
Antipsychotics	Efficacy is impaired by phenytoin
Furosemide	Efficacy is impaired by phenytoin
Quinidine	Efficacy is impaired by phenytoin
Theophylline	Efficacy is impaired by phenytoin
Vitamin D	Efficacy is impaired by phenytoin
FRAMYCETIN	
Capreomycin	Additive toxicity with capreomycin
FURAZOLIDONE	
SSRIs	Risk of serotonin syndrome
FUROSEMIDE	
Amphotericin B	Increased risk of hypokalaemia
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Digoxin	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Enalapril	Enhanced hypotensive effect
Glibenclamide	Antagonism of hypoglycaemic effect

Corticosteroids	Antagonism of diuretic effect; increased risk of hypokalaemia
Lithium	Increased plasma-lithium concentration and risk of toxicity
Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol
Streptomycin	Increased risk of ototoxicity
Vancomycin	Increased risk of ototoxicity
GEMCITABINE	
Live vaccines	Serum antibody response may not be obtained
Zidovudine	Additive toxicity
GENTAMICIN	
Cyclosporine	Increased risk of nephrotoxicity
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Suxamethonium	Enhanced muscle relaxant effect
Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Vecuronium	Enhanced muscle relaxant effect
GLIBENCLAMIDE	
Ciprofloxacin	Enhanced effect of glibenclamide
Corticosteroids	Antagonism of hypoglycaemic effect
Enalapril	Hypoglycaemic effect enhanced
Fluconazole	Plasma concentration of glibenclamide increased
Hydrochlorothiazide	Antagonism of hypoglycaemic effect
Levonorgestrel	Antagonism of hypoglycaemic effect
Sulfadoxine + Pyrimethamine	Effect of glibenclamide may be enhanced
Sulfamethoxazole + Trimethoprim	Effect of glibenclamide may be enhanced
Warfarin	Enhanced hypoglycaemic effects and changes to anticoagulant effect

GLICLAZIDE	
Acetylsalicylic acid	Effect of gliclazide is potentiated
Clofibrate	Effect of gliclazide is potentiated
Sulphonamides	Effect of gliclazide is potentiated
Oral anticoagulants	Effect of gliclazide is potentiated
MAO inhibitors	Effect of gliclazide is potentiated
Rifampicin	Effect of gliclazide is antagonized
Barbiturates	Effect of gliclazide is antagonized
Diuretics	Effect of gliclazide is antagonized
Diazoxide	Effect of gliclazide is antagonized
Glucocorticoids	Effect of gliclazide is antagonized
Sympathomimetics	Effect of gliclazide is antagonized
GLIMEPIRIDE	
Corticosteroids	Reduced hypoglycaemic action
Phenytoin	Reduced hypoglycaemic action
Thiazides	Reduced hypoglycaemic action
GLUCAGON	
Anticoagulants	Excess hypoprothrombinemia and bleeding complications
GLYCERYL TRINITRATE	
Atenolol	Enhanced hypotensive effect
Corticosteroids	Antagonism of hypotensive effect
GRISEOFULVIN	
Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Warfarin	Metabolism of warfarin accelerated (reduced anticoagulant effect)

HALOPERIDOL	
Amitriptyline	Increased plasma-amitriptyline concentration; increased risk of ventricular arrhythmias
Carbamazepine	Antagonism of anticonvulsant effect, metabolism of haloperidol accelerated
Lithium	Increased risk of extrapyramidal effects and neurotoxicity
Metoclopramide	Increased risk of extrapyramidal effects
Phenobarbital	Antagonism of anticonvulsant effect, metabolism of haloperidol accelerated
Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Rifampicin	Accelerated metabolism of haloperidol (reduced plasma-haloperidol concentration)
Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
HALOTHANE	
Amitriptyline	Increased risk of arrhythmias and hypotension
Atenolol	Enhanced hypotensive effect
Diazepam	Enhanced sedative effect
Levodopa	Risk of arrhythmias
Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
Verapamil	Enhanced hypotensive effect and AV delay
HEPARIN	
Acetylsalicylic acid	Enhanced anticoagulant effect
Enalapril	Increased risk of hyperkalaemia
HYDRALAZINE	
Corticosteroids	Antagonism of hypotensive effect

HYDROCHLOROTHIAZIDE

Amitriptyline	Increased risk of postural hypotension
Amphotericin B	Increased risk of hypokalaemia
Artemether + Lumefantrine	Increased risk of ventricular arrhythmias if electrolyte disturbance occurs
Carbamazepine	Increased risk of hyponatraemia
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Digoxin	Cardiac toxicity of digoxin increased if hypokalaemia occurs
Glibenclamide	Antagonism of hypoglycaemic effect
Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Insulins	Antagonism of hypoglycaemic effect
Lithium	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol

IBUPROFEN

Acetylsalicylic acid	Avoid concurrent administration (increased adverse effects, including gastrointestinal damage); antiplatelet effect of acetylsalicylic acid reduced
Atenolol	Antagonism of hypotensive effect
Cyclosporine	Increased risk of nephrotoxicity
Ciprofloxacin	Increased risk of convulsions
Corticosteroids	Increased risk of gastrointestinal bleeding and ulceration
Digoxin	Exacerbation of heart failure, reduced GFR, and increased plasma-digoxin concentration
Enalapril	Antagonism of hypotensive effect, increased risk of renal impairment

Glibenclamide	Enhanced effect of glibenclamide
Hydrochlorothiazide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Lithium	Reduced excretion of lithium
Methotrexate	Excretion of methotrexate reduced
Nifedipine	Antagonism of hypotensive effect
Warfarin	Anticoagulant effect enhanced
Zidovudine	Increased risk of haematological toxicity
IMATINIB	
Rifampin	Increased clearance of imatinib
Warfarin	Imatinib may inhibit metabolism of warfarin
IMIPENEM + CILASTATIN	
Ganciclovir	May result in generalised seizures
INDINAVIR	
Carbamazepine	Reduced plasma concentration of indinavir
Efavirenz	Reduced plasma concentration of indinavir
Ergotamine	Increased risk of ergotism (avoid concomitant use)
Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both)
Nevirapine	Reduced plasma concentration of indinavir
Phenobarbital	Reduced plasma concentration of indinavir
Rifampicin	Metabolism enhanced by rifampicin
INSULINS	
Atenolol	Enhanced hypoglycaemic effect; masking of warning signs of hypoglycaemia such as tremor
Corticosteroids	Antagonism of hypoglycaemic effect

Enalapril	Hypoglycaemic effect enhanced
Furosemide	Antagonism of hypoglycaemic effect
Hydrochlorothiazide	Antagonism of hypoglycaemic effect
Levonorgestrel	Antagonism of hypoglycaemic effect
Nifedipine	Occasionally impaired glucose tolerance
IODINE	
Lithium	Synergistic toxicity
IOPANOIC ACID	
Atenolol	Iopanoic acid toxicity may occur
Methotrexate	Methotrexate toxicity may occur
ISONIAZID	
Carbamazepine	Increased plasma-carbamazepine concentration
Diazepam	Metabolism of diazepam inhibited
Phenytoin	Metabolism of phenytoin inhibited
ISOSORBIDE DINITRATE	
Sildenafil	Serious hypotension, MI may be precipitated
ISOTRETINOIN	
Vitamin A	Additive toxicity
Progesterone	Decreased efficacy of microdosed progesterone
Corticosteroids, phenytoin	Increased risk of osteoporosis
Carbamazepine	Decreased plasma levels of carbamazepine
Tetracyclines	Increased risk of pseudotumor cerebri
ISPAGHULA	
Lithium	Decreased effect of lithium
IVERMECTIN	
Vitamin K Antagonists (eg, warfarin)	Enhanced anticoagulant effect

KETOCONAZOLE	
Amphotericin B	Increased adverse effect
Cyclosporine	Increased level of cyclosporine
Tolbutamide	Reduces blood glucose level
LAMIVUDINE	
Foscarnet	Concurrent use not recommended
LATANOPROST	
Thiomersal	Risk of precipitate formation
LEFLUNOMIDE	
Acenocoumarol	Increased anticoagulant effect
Warfarin	Increased anticoagulant effect
Methotrexate	Increased risk of hepatotoxicity
Cholestyramine	Enhanced leflunomide excretion and increased total clearance by approximately 50%
LEVOCETIRIZINE	
Alcohol or CNS depressants	Additive sedation
Theophylline	Increases the levels of levocetirizine in blood
LEVODOPA	
Metoclopramide	Antagonism of effects of levodopa
Ether, Anaesthetic	Risk of arrhythmias
Ferrous salts	Absorption of levodopa may be reduced
Halothane	Risk of arrhythmias
Methyldopa	Enhanced hypotensive effect; antagonism of antiparkinsonian effect
Nifedipine	Enhanced hypotensive effect
Propranolol	Enhanced hypotensive effect
Pyridoxine	Antagonism of levodopa unless carbidopa also given
LEVOTHYROXINE	
Phenobarbital	Metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism)

Theophylline	Metabolism of theophylline is increased; larger doses are required
Warfarin	Enhanced anticoagulant effect
LIDOCAINE	
Acetazolamide	Action of lidocaine antagonised by hypokalaemia
Atenolol	Increased risk of myocardial depression
Bupivacaine	Increased myocardial depression
Furosemide	Action of lidocaine antagonised by hypokalaemia
Hydrochlorothiazide	Action of lidocaine antagonised by hypokalaemia
Procainamide	Increased myocardial depression
Propranolol	Increased risk of myocardial depression; increased risk of lidocaine toxicity
Quinidine	Increased myocardial depression
Timolol	Increased risk of myocardial depression
Verapamil	Increased risk of myocardial depression
LITHIUM	
Acetazolamide	Excretion of lithium increased
Amiloride	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity)
Enalapril	Enalapril reduces excretion of lithium (increased plasma-lithium concentration)
Furosemide	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
Haloperidol	Increased risk of extrapyramidal effects and possibility of neurotoxicity
Hydrochlorothiazide	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide

Ibuprofen	Reduced excretion of lithium (risk of toxicity)
Methyldopa	Neurotoxicity may occur without increased plasma-lithium concentration
Spironolactone	Reduced lithium excretion (increased plasma-lithium concentration and risk of toxicity)
Suxamethonium	Enhanced muscle relaxant effect
LOPERAMIDE	
Quinidine	Increased CNS level of loperamide
MEBENDAZOLE	
Carbamazepine	Reduced plasma-mebendazole concentration (increase mebendazole dose for tissue infection)
Phenytoin	Reduced plasma-mebendazole concentration (increase mebendazole dose for tissue infection)
MEFENAMIC ACID	
Warfarin	Risk of serious GI bleeding higher than users of either drug alone.
Lithium	Reduced renal clearance and increased risk of lithium toxicity.
Methotrexate	Reduced excretion of methotrexate and possible increased risk of toxicity
Phenobarbital	Reduced plasma-mebendazole concentration (increase mebendazole dose for tissue infection)
6-MERCAPTOPURINE	
Allopurinol	Effects of 6-mercaptopurine enhanced with increased toxicity, reduce dose when given with allopurinol
Phenytoin	Reduced absorption of phenytoin
Sulfamethoxazole + Trimethoprim	Increased risk of haematological toxicity

Sulfasalazine	Increased risk of leukopenia
Trimethoprim	Increased risk of haematological toxicity
Vaccines, Live	Avoid use of live vaccines with 6-mercaptopurine (impairment of immune response)
Warfarin	Anticoagulant effect reduced
MEROPENEM	
Probenecid	Renal excretion of meropenem is inhibited
Valproic acid	Serum valproic acid concentration is decreased
METFORMIN	
Atenolol	Masking of warning signs of hypoglycaemia such as tremor
Corticosteroids	Antagonism of hypoglycaemic effect
Enalapril	Hypoglycaemic effect enhanced
Levonorgestrel	Antagonism of hypoglycaemic effect
Lithium	May occasionally impair glucose tolerance
Medroxyprogesterone	Antagonism of hypoglycaemic effect
Norethisterone	Antagonism of hypoglycaemic effect
METHADONE	
Cimetidine	Effect of methadone may be increased
MAO Inhibitors	Risk of hypotension, hyperexia etc.
METHOTREXATE	
Acetylsalicylic acid	Reduced excretion of methotrexate (increased toxicity)
Amoxycillin	Reduced excretion of methotrexate (increased risk of toxicity)
Cyclosporine	Increased toxicity
Ibuprofen	Excretion of methotrexate reduced (increased risk of toxicity)

Nitrous oxide	Increased antifolate effect (avoid concomitant use)
Phenytoin	Reduced absorption of phenytoin; antifolate effect of methotrexate increased
Pyrimethamine	Antifolate effect of methotrexate increased
Sulfadoxine + Pyrimethamine	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
Sulfamethoxazole + Trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased
Trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use)
Vaccines, Live	Avoid use of live vaccines with methotrexate (impairment of immune response)
METHYLDOPA	
Ferrous salts	Reduced hypotensive effect of methyldopa
Propranolol	Enhanced hypontensive effect
METHYL PREDNISOLONE	
Amphotericin B	Chances of potentiation of K+ concentration
Cyclosporine	Levels increased upto 2 fold
METRONIDAZOLE	
Phenytoin	Metabolism of phenytoin inhibited (increased plasma-phenytoin concentration)
Warfarin	Enhanced anticoagulant effect
MMR vaccine	See vaccines, live
MIDAZOLAM	
Ketoconazole	Increased levels of midazolam
Verapamil	Increased levels of midazolam
MIFEPRISTONE	
Dexamethasone	Decreased serum levels of mifepristone

MOMETASONE	
Anticoagulants	Increased or decreased effects of anticoagulants
Bupropion	Increased risk of seizures
Quinolones	Increased risk of tendonitis and/or tendon rupture
Quetiapine	Decreased levels of quetiapine
MORPHINE	
Ciprofloxacin	Avoid premedication with morphine (reduced plasma-ciprofloxacin concentration)
Quinidine	Decreased analgesic effect
Ritonavir	Ritonavir increases plasma concentration of morphine
MYCOPHENOLATE	
Bile acid sequestrants	Decreased level and clinical effect of mycophenolate
Antacids	Decreased effect
NALIDIXIC ACID	
Cyclosporine	Increased risk of nephrotoxicity
Ibuprofen	Increased risk of convulsions
Theophylline	Increased risk of convulsions
Warfarin	Enhanced anticoagulant effect
NELFINAVIR	
Ergotamine	Increased risk of ergotism (avoid concomitant use)
Phenobarbital	Plasma concentration of nelfinavir reduced
Quinidine	Increased risk of ventricular arrhythmias (avoid concomitant use)
Rifampicin	Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)
NEOSTIGMINE	
Gentamicin	Antagonism of effect of neostigmine
Streptomycin	Antagonism of effect of neostigmine

NEVIRAPINE	
Lopinavir	Plasma concentration of lopinavir reduced
Rifampicin	Reduced plasma concentration of nevirapine (avoid concomitant use)
Saquinavir	Plasma concentration of saquinavir reduced (avoid concomitant use)
NICOTINIC ACID	
Ganglionic blocking agents and vasoactive drugs	Potentiates the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension
Bile acid sequestrants (for example, cholestyramine)	Bind and prevent absorption of niacin, should be separated by 4-6 hours.
NIFEDIPINE	
Atenolol	Severe hypotension and heart failure occasionally
Cyclosporine	Increased plasma-nifedipine concentration (increased risk of adverse effects such as gingival hyperplasia)
Digoxin	Increased plasma concentration of digoxin
Magnesium (parenteral)	Profound hypotension reported with nifedipine and intravenous magnesium sulphate in pre-eclampsia
Phenobarbital	Effect of nifedipine reduced
Phenytoin	Reduced effect of nifedipine
Propranolol	Severe hypotension and heart failure occasionally
Ritonavir	Plasma concentration increased by ritonavir
Rifampicin	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
Theophylline	Enhanced theophylline effect (increased plasma-theophylline concentration)

Timolol	Severe hypotension and heart failure occasionally
NITROUS OXIDE	
Chlorpromazine	Enhanced hypotensive effect
Fluphenazine	Enhanced hypotensive effect
Haloperidol	Enhanced hypotensive effect
Methotrexate	Increased antifolate effect (avoid concomitant use)
Verapamil	Enhanced hypotensive effect and AV delay
NORADRENALINE	
Guanethidine + methyldopa + reserpine + tricyclic antidepressants	Pressor response to norepinephrine may be increased
Cocaine	Increased risk of arrhythmias
MAOIs	Hypertensive crisis occurs
Nonselective β-blockers	Increased hypertensive effects
OMEPRAZOLE	
Cilostazol	Increased levels of cilastazole
Nelfinavir	Decreased level of nelfinavir
Raltegravir	Increased levels of raltigavir
ONDANSETRON	
Tramadol	Decreased effectiveness of tramadol.
OXCARBAMAZEPINE	
Lamotrigine	Decreased levels of lamotrigine
OXYTETRACYCLINE	
Calcium and Iron dextran	Formation of non-absorbable complexes
Penicillins	Antagonism of effect of oxytetracycline
Etritenate and isotretinoin	Associated with increased risk of intracranial hypertension
Oral contraceptives	May decrease the effect of oral contraceptives.
PHENOBARBITAL	

Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline accelerated (reduced plasma concentration)
Carbamazepine	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine often lowered
Cyclosporine	Metabolism of cyclosporine accelerated (reduced effect)
Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Nifedipine	Effect of nifedipine reduced
Phenytoin	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised
Valproic acid	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; phenobarbital concentration often raised
Warfarin	Metabolism of warfarin accelerated (reduced anticoagulant effect)
PHENOXYMETHYL PENICILLIN	
Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
PHENYTOIN	
Amitriptyline	Antagonism (convulsive threshold lowered); reduced plasma-amitriptyline concentration
Carbamazepine	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered

Chloramphenicol	Plasma-phenytoin concentration increased (risk of toxicity)
Chloroquine	Convulsive threshold occasionally lowered
Cyclosporine	Accelerated metabolism (reduced plasma-cyclosporine concentration)
Clonazepam	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of clonazepam often lowered
Fluconazole	Effect of phenytoin enhanced; plasma concentration increased
Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Isoniazid	Metabolism of phenytoin inhibited (enhanced effect)
Mefloquine	Antagonism of anticonvulsant effect
Metronidazole	Metabolism of phenytoin inhibited (increased plasma-phenytoin concentration)
Nifedipine	Reduced effect of nifedipine
Pyrimethamine	Antagonism of anticonvulsant effect; increased antifolate effect
Rifampicin	Accelerated metabolism of phenytoin (reduced plasma concentration)
Sulfadoxine + Pyrimethamine	Plasma-phenytoin concentration increased; increased antifolate effect
Sulfamethoxazole + Trimethoprim	Antifolate effect and plasma-phenytoin concentration increased
Valproic acid	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of phenytoin often raised (but may also be lowered)

Warfarin	Accelerated metabolism of warfarin (Reduced anticoagulant effect, but enhancement also reported)
PIOGLITAZONE	
NSAID	Increased risk of fluid retention
Rifampicin	Decreased plasma concentration.
Ketoconazole	Increased plasma concentration.
PIPERACILLIN + TAZOBACTAM	
Aminoglycosides	Inactivation of aminoglycosides
Methotrexate	Reduced clearance of methotrexate
PREDNISOLONE	
Amphotericin B	Increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions)
Carbamazepine	Accelerated metabolism of prednisolone (reduced effect)
Phenobarbital	Metabolism of prednisolone accelerated (reduced effect)
Phenytoin	Metabolism of prednisolone accelerated (reduced effect)
Rifampicin	Accelerated metabolism of prednisolone (reduced effect)
Vaccines, Live	High doses of prednisolone impair immune response; avoid use of live vaccines
Warfarin	Anticoagulant effect altered
PROPOFOL	
Fentanyl	Concomitant use in pediatric patients may result in serious bradycardia
CNS depressants	Increased sedative, anaesthetic and cardiorespiratory effects
PYRIDOXINE	
Levodopa	Antagonism of levodopa unless carbidopa also given
PYRIMETHAMINE	
Artemether + Lumefantrine	Avoid concomitant use

Methotrexate	Antifolate effect of methotrexate increased
Phenytoin	Antagonism of anticonvulsant effect; increased antifolate effect
Sulfonamides + Trimethoprim	Increased antifolate effect
RALOXIFENE	
Estrogen	Increased risk of adverse effects.
RAMIPRIL	
Diuretics	Excessive reduction of blood pressure
Potassium supplements/ Potassium sparing diuretics	Increased risk of hyperkalemia
Lithium	Increased serum lithium levels and lithium toxicity
RIFAMPICIN	
Azathioprine	Transplants rejected
Cyclosporine	Accelerated metabolism (reduced plasma-cyclosporine concentration)
Dapsone	Reduced plasma-dapsone concentration
Fluconazole	Accelerated metabolism of fluconazole (reduced plasma concentration)
Glibenclamide	Accelerated metabolism (reduced effect) of glibenclamide
Haloperidol	Accelerated metabolism of haloperidol (reduced plasma-haloperidol concentration)
Nifedipine	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
Phenytoin	Accelerated metabolism of phenytoin (reduced plasma concentration)
Corticosteroids	Accelerated metabolism of corticosteroids
Verapamil	Accelerated metabolism of verapamil (plasma concentration significantly reduced)

Warfarin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
RITONAVIR	
Carbamazepine	Plasma concentration increased by ritonavir
Cyclosporine	Plasma concentration increased by ritonavir
Diazepam	Plasma concentration increased by ritonavir (risk of extreme sedation and respiratory depression-avoid concomitant use)
Fluconazole	Plasma concentration increased by ritonavir
Verapamil	Plasma concentration increased by ritonavir
Warfarin	Plasma concentration increased by ritonavir
SALBUTAMOL	
Methyldopa	Acute hypotension reported with salbutamol infusion
SILDENAFIL	
Protease inhibitors	Sildenafil metabolism is inhibited
Alpha blockers	Avoid concomitant use (may lead to low blood pressure)
Ketoconazole	Increased action of sildenafil
Erythromycin	Increased action of sildenafil
Verapamil	Increased action of sildenafil
Nitrates	Vasoconstrictor activity of nitrates is potentiated
STREPTOMYCIN	
Amphotericin B	Increased risk of nephrotoxicity
Cyclosporine	Increased risk of nephrotoxicity
Cisplatin	Increased risk of nephrotoxicity and ototoxicity
Furosemide	Increased risk of ototoxicity
Neostigmine	Antagonism of effect of neostigmine
Suxamethonium	Enhanced muscle relaxant effect

STRONTIUM RANELATE

Calcium products	Reduced biovailability of strontium ranelate.
Tetracycline	Reduced absorption of oral tetracycline
Quinolone antibiotics	Reduced absorption of quinolone antibiotics
Almunium and Magnesium Hydroxides	Decreased absorption of strontium ranelate.

SULFADOXINE + PYRIMETHAMINE

Artemether + Lumefantrine	Avoid concomitant use
Cyclosporine	Increased risk of nephrotoxicity
Glibenclamide	Effect of glibenclamide rarely, enhanced
Methotrexate	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
Phenytoin	Plasma-phenytoin concentration increased; increased antifolate effect
Warfarin	Enhanced anticoagulant effect

SULFASALAZINE

Azathioprine	Increased risk of leukopenia
Mercaptopurine	Increased risk of leukopenia

TACROLIMUS

Aminoglycosides	Increased risk of renal dysfunction
Carbamazepine	Decreased tacrolimus blood concentration
Cisplatin	Increased risk of renal dysfunction
Clarithromycin	Increased tacrolimus blood concentration
Chloramphenicol	Increased tacrolimus blood concentration
Clotrimazole	Increased tacrolimus blood concentration
Phenytoin	Decreased tacrolimus blood concentration
Rifampin	Decreased tacrolimus blood concentration

Diltiazem	Increased tacrolimus blood concentration
Nifedipine	Increased tacrolimus blood concentration
Verapamil	Increased tacrolimus blood concentration

TELMISARTAN

Lithium	Increased in serum lithium concentration and toxicity

THALIDOMIDE

Barbiturates	Enhanced sedative activity
Alcohol	Enhanced sedative activity
Chlorpromazine	Enhanced sedative activity
Reserpine	Enhanced sedative activity
Vincristine	Potential to cause peripheral neuropathy
Bortezomib	Potential to cause peripheral neuropathy

THEOPHYLLINE

Ciprofloxacin	Increased plasma-theophylline concentration; increased risk of convulsions
Erythromycin	Inhibition of theophylline metabolism (increased plasma-theophylline concentration resulting in theophylline toxicity)
Fluconazole	Plasma-theophylline concentration increased

TIMOLOL

Note: Systemic absorption may follow topical application of timolol to the eye

Epinephrine	Severe hypertension
Verapamil	Asystole, severe hypotension and heart failure

TOPIRAMATE

Carbamazepine	Reduced plasma level of topiramate
Phenytoin	Reduced plasma level of topiramate
Rifampin	Reduced plasma level of topiramate

TRANEXAMIC ACID	
Clotting factor complexes	Increased risk of thrombotic complications
Hormonal contraception	Exacerbate the increased thrombotic risk associated with combination hormonal contraceptives
all-trans Retinoic acid	Concomitant use in women with acute promyelocytic leukemia taking all-trans retinoic acid for remission induction may cause exacerbation of the procoagulant effect of all-trans retinoic acid
TRIMETHOPRIM	
Mercaptopurine	Increased risk of haematological toxicity
Methotrexate	Antifolate effect of methotrexate increased (avoid concomitant use)
Phenytoin	Antifolate effect and plasma-phenytoin concentration increased
Pyrimethamine	Increased antifolate effect
Sulfadoxine + Pyrimethamine	Increased antifolate effect
VALPROIC ACID	
Carbamazepine	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of active metabolite of carbamazepine often raised
Chloroquine	Convulsive threshold occasionally lowered
Mefloquine	Antagonism of anticonvulsant effect
Phenobarbital	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; phenobarbital concentration often raised

Phenytoin	Enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid often lowered; plasma concentration of phenytoin often raised (but may also be lowered)
VANCOMYCIN	
Cyclosporine	Increased risk of nephrotoxicity
Furosemide	Increased risk of ototoxicity
VARICELLA VACCINE	
Salicylates	Increased risk of Reye's syndrome
VERAPAMIL	
Atenolol	Asystole, severe hypotension and heart failure
Carbamazepine	Enhanced effect of carbamazepine
Digoxin	Increased plasma concentration of digoxin; increased AV block and bradycardia
Halothane	Enhanced hypotensive effect and AV delay
Ketamine	Enhanced hypotensive effect and AV delay
Lidocaine	Increased risk of myocardial depression
Rifampicin	Accelerated metabolism of verapamil (plasma concentration significantly reduced)
VINBLASTINE	
Bleomycin	Increased risk of cardiovascular toxicity
WARFARIN	
Acetylsalicylic acid	Increased risk of bleeding due to antiplatelet effect
Azathioprine	Anticoagulant effect reduced
Azithromycin	Enhanced anticoagulant effect of warfarin
Carbamazepine	Accelerated metabolism of warfarin (reduced anticoagulant effect)

Ceftazidime	Enhanced anticoagulant effect
Ceftriaxone	Enhanced anticoagulant effect
Chloramphenicol	Enhanced anticoagulant effect
Ciprofloxacin	Enhanced anticoagulant effect
Corticosteroids	Anticoagulant effect altered
Doxycycline	Anticoagulant effect enhanced
Erythromycin	Enhanced anticoagulant effect
Fluconazole	Enhanced anticoagulant effect
5-Fluorouracil	Anticoagulant effect enhanced
Glibenclamide	Enhanced hypoglycaemic effects and changes to anticoagulant effect
Griseofulvin	Metabolism of warfarin accelerated (reduced anticoagulant effect)
Ibuprofen	Anticoagulant effect enhanced
Levamisole	Anticoagulant effect enhanced
Levonorgestrel	Antagonism of anticoagulant effect
Levothyroxine	Enhanced anticoagulant effect
Medroxyprogesterone	Antagonism of anticoagulant effect
Mercaptopurine	Anticoagulant effect reduced
Metronidazole	Enhanced anticoagulant effect
Nalidixic acid	Enhanced anticoagulant effect
Norethisterone	Antagonism of anticoagulant effect
Ofloxacin	Enhanced anticoagulant effect
Phenobarbital	Metabolism of warfarin accelerated (reduced anticoagulant effect)
Phenytoin	Accelerated metabolism of warfarin (reduced anticoagulant effect, but enhancement also reported)
Phytomenadione	Antagonism of anticoagulant effect by phytomenadione
Proguanil	Isolated reports of enhanced anticoagulant effect

Quinidine	Anticoagulant effect may be enhanced
Rifampicin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
Ritonavir	Plasma concentration increased by ritonavir
Sulfadiazine	Enhanced anticoagulant effect
Sulfadoxine + Pyrimethamine	Enhanced anticoagulant effect
Sulfamethoxazole + Trimethoprim	Enhanced anticoagulant effect
Tamoxifen	Enhanced anticoagulant effect
ZIDOVUDINE	
Fluconazole	Increased plasma concentration of zidovudine (increased risk of toxicity)
Stavudine	May inhibit effect of stavudine (avoid concomitant use)
ZOLPIDEM	
Rifampin	Pharmacodynamic effects of zolpidem are decreased
Ketoconazole	Pharmacodynamic effects of zolpidem are increased

Appendix 6d:
Drug – Food Interactions

Several drugs when given orally can interact with food consumed by the patients. Table 1 shows the medications which should be taken on an empty stomach.

Table 1: Medications which should be taken on an EMPTY stomach

Drug	Food interactions and effect
Ampicillin	Reduced absorption
Alendronate	Decreased bioavailability
Azithromycin	Reduced absorption
Bisacodyl	Dissolves enteric coating
Didanosine	Decreased absorption
Indinavir	Reduced absorption with fat, proteins
Isoniazid	Reduced absorption
Isosorbide dinitrate	Delayed absorption
Levothyroxine	Reduced absorption; anionic exchange resins reduce absorption
Melphalan	Reduced absorption
Methotrexate	Reduced absorption
Mycophenolate	Enhanced absorption
Omeprazole	Delayed absorption
Oxytetracycline	Reduced absorption when taken with dairy products.
Rifampin	Delayed absorption
Roxithromycin	Reduced absorption
Sulfadiazine	Formation of crystalluria on consumption with vitamin C or acidifying agents
Tacrolimus	Reduced absorption
Tetracycline	Reduced absorption, especially when taken with antacids or dairy products
Thyroid	Reduced absorption

Typhoid vaccine (oral)	Reduced absorption
Zidovudine	Enhanced absorption

Food can also impact the effectiveness of a drug due to the way it is consumed. Generally, medicine is to be taken almost at the same time the food is eaten. This is because the medicine may upset the stomach if the stomach is empty. Certain medications are recommended to be taken with food (Table 2).

Table 2: Medications which should be taken WITH FOOD

Drug	Food interactions and effect
Acetylsalicylic Acid	Reduced side effects.
Allopurinol	Reduced side effects; reduced clearance of active metabolite with protein-poor diet
Amiodarone	Enhances both the rate and extent of absorption.
Amoxycillin/clavulanic acid	Reduced side effects
Azathioprine	Reduced side effects
Baclofen	Reduced side effects
Bromocriptine	Reduced side effects
Carbamazepine	Increased absorption
Cefuroxime	Increased absorption
Chloroquine	Reduced side effects
Clofazimine	Increased drug absorption
Conjugated estrogens	Reduced side effects
Diclofenac	Reduced peak concentration but not extent of absorption; reduced side effects
Doxycycline	Reduced side effects; reduced absorption with milk
Ethinyl estradiol	Reduced side effects
Ferrous salts	Take between meals, if gastrointestinal upset occurs take with food
Griseofulvin	Increased rate or extent of absorption with fats; reduced side effects
Hydroxychloroquine	Reduced bowel side effects; masks the bitter taste of drug
Hydrocortisone	Slows rate of absorption; reduced peak levels; reduced side effects

Ibuprofen	Reduced side effects
Iron preparations	See ferrous salts
Levocetirizine	May be taken with or without food
Lithium	Reduced side effects
Mebendazole	Increased absorption
Methadone	Reduced side effects
Methylprednisolone	Reduced side effects
Metronidazole	Reduced side effects
Mexiletine	Reduced side effects; slows rate of absorption; reduces rate of caffeine clearance
Morphine	Increased absorption
Nelfinavir	Greatly increases absorption and AUC
Niacin	Reduced absorption; decreases side effects
Nitrofurantoin	Increased absorption
Pioglitazone	Food slightly delays absorption rate but extent of absorption is not affected.
Potassium salts	Reduced side effects
Prednisolone	Reduced side effects
Prednisone	Reduced stomach irritation
Procainamide	Reduced side effects; increased absorption with fat
Propranolol	Slows rate but increases extent of absorption
Quinine	Reduced side effects
Ritonavir	Increased absorption
Salsalate	Reduced stomach irritation.
Saquinavir	Increased absorption.

Sodium chloride	Reduced side effects
Spironolactone	Increased absorption; reduced side effects
Sulfasalazine	Reduced side effects
Sodium valproate	Reduced side effects

Table 3: Selected herbal or food products resulting in adverse effects

Herb/Food	Drug	Adverse Effects/Reported Drug Interactions/ Remark
Licorice	Digoxin Spironolactone	Elevates serum digoxin levels 4-fold, arrhythmias Hypokalemia and muscle weakness
Foods high in vitamin K (broccoli, sprouts, turnip greens, spinach, cauliflower, legumes, mayonnaise, soybean oils and fish	Anticoagulants (warfarin)	Such foods may reduce the effectiveness of anticoagulants, increasing the risk of clotting. Intake of such foods should be limited, and the amount consumed daily should remain constant.
Foods high in sodium (like licorice, processed meats, canned foods)	Amlodipine	Such foods decrease the effectiveness of the drug
Calcium or foods containing calcium (milk and other dairy products)	Tetracycline	These foods can reduce the absorption of tetracycline, which should be taken 1 hr before or 2 hr after eating
Foods high in tyramine, (includes cheese, yoghurt, sour cream, cured meats, liver, dried fish, bananas, yeast extracts, raisins, soya sauce, red wine, certain beers)	MAO - inhibitors (such as phenelzine and tranylcypromine)	Severe headache and a potentially fatal increase in BP (hypertensive crisis) can occur if people taking MAO - inhibitors consume these foods. These foods must be avoided.

Appendix 7a: Hepatic Impairment

Dosing considerations in hepatic impairment

Hepatobiliary system plays an important role in the interactions between drugs and the body. Liver diseases can affect pharmacokinetics and pharmacodynamics of various drugs. However there has to be moderate to severe hepatic impairment to significantly alter the response to drugs as liver has a large reserve capacity. Hepatic impairment may alter response to drugs not only because of its role in metabolism of drugs but it also affects their absorption and distribution. Looking at the importance of liver in dealing with the drug, knowledge of a patient's hepatic function is required for the safe prescribing of many drugs. Unlike renal disease, where estimation of renal function based on creatinine clearance can fairly help in knowing the drug elimination and hence dose adjustment, there is no endogenous marker for hepatic clearance that can be used as a guide for drug dosing.

Hepatic impairment can lead to altered response to drugs due to all or some of the following reasons:

- Metabolism of many drugs depend on adequate liver function. Generally, metabolism result in the loss of pharmacological activity and therefore reduced metabolism in case of impaired liver function can lead to the accumulation of drug in the body to the toxic level at the normal dose. However in some cases drugs are metabolised to the active form and in these drugs normal dose may not be able to achieve desired response.
- For drugs with low bioavailability (high hepatic extraction), bioavailability increases and hepatic clearance decreases in cirrhotic patients. If such drug is to be administered orally to cirrhotic patients, their initial dose has to be reduced according to their hepatic extraction. For drugs with low bioavailability (low hepatic extraction), hepatic clearance may be affected due to impaired metabolism. For such drugs only the maintenance dose has to be adjusted according to estimated decrease in their hepatic metabolism.
- Portal hypertensive gastropathy and ulcers of upper gastrointestinal tract, frequently seen in cirrhotic patients may alter the absorption of orally administered drugs. Absorption of drugs may be increased because of high intestinal permeability in patients

with portal hypertension. Impaired gastrointestinal motility seen in cirrhotic patients can lead to delayed drug absorption

- Volume of distribution of hydrophilic drugs is increased due to presence of oedema and/or ascitis. Hence, loading dose of these drugs may have to be increased if a rapid action is required. On the other hand increase in volume of distribution is associated with an increase in the elimination half life of such drugs.
- Impaired elimination of drugs which are excreted in the bile can lead to their accumulation in the body.
- Impaired albumin production can lead to decreased protein binding and increased toxicity of highly plasma protein bound drugs.
- High percentage of drugs may reach systemic circulation without passing through liver due to development of portosystemic shunts in cirrhotic patients.
- Cirrhotic patients can often have impaired renal function and in these cases dosage of the drugs have to be carefully adjusted.

The use of certain drugs in patients with cirrhosis may increase the risk of hepatic decompensation. In patients with impaired liver function dose related hepatotoxic reaction may occur at lower doses. Drugs that cause fluid retention (for example, prednisolone, ibuprofen, dexamethasone etc.) may exacerbate oedema and ascitis in chronic liver disease. Sensitivity of brain to depressant action of some drugs(for example, morphine and barbiturates) is markedly increased in cirrhotic patients and can precipitate hepatic encephalopathy at normal doses.

As evident from above, there is a complex interactions between the drugs and liver function. Absence of any endogenous marker for hepatic clearance makes it highly difficult to accurately adjust the dose of various drugs in hepatic impairment. Therefore, if no immediate pharmacological effect is needed, drug therapy should be started cautiously in these patients and titrated individually until desired effect is achieved or toxicity appears. Drugs with a narrow therapeutic range and low hepatic extraction for e.g. theophylline are the most dangerous drugs. If such drugs are administered orally, both loading dose and maintenance doses have to be reduced by ≥ 50% of the normal dose, depending on the severity of hepatic impairment.

The following table contains information to help prescribing

common drugs in hepatic impairment. The table provided is not exhaustive and abscence from this table does not imply safety of drug, it is therefore important to refer to the individual drug entries.

Drug	Status	Comments
Abacavir	Avoid in severe hepatic impairment	Avoid in moderate hepatic impairment unless essential
Acetylsalicylic acid	Avoid in severe hepatic impairment	Increased risk of Gastrointestinal bleeding
Allopurinol	Reduce the dose	
Aluminium hydroxide	Avoid in severe hepatic impairment	Can precipitate hepatic encephalopathy by causing constipation. Antacids containing high amount of sodium to be avoided in patients with fluid retention.
Amidotrizoate	Use with caution	
Amitryptyline	Avoid in severe hepatic impairment	Increased sedation
Amlodipine	Reduce dose	Half life of a mlodipine is prolonged
Amodiaquine	Avoid in hepatic impairment	
Amoxycillin + Clavulanic acid	Use with caution	Monitor liver function, cholestatic jaundice reported either during or shortly after therapy (more common in males and patients over 65 years), duration of treatment should not exceed 2 weeks.
Azathioprine	Reduce dose	
Azithromycin	Avoid	May cause jaundice
Bupivacaine	Avoid or reduce dose in severe hepatic impairment	
Carbamazepine	Avoid in severe moderate to severe hepatic impairment	Cautiously given in mild hepatic impairment
Ceftriaxone	Reduce dose and monitor plasma concentration if there is associated renal impairment	
Chlorambucil	Reduce dose and use cautiously in hepatic impairment	

Chloramphenicol	Avoid if possible, reduce dose and monitor plasma concentration	Increased risk of bone marrow depression
Chlorpheniramine	Avoid	May cause inappropriate sedation
Chlorpromazine	Use with caution	May precipitate coma
Clindamycin	Reduce dose	
Clomifene	Avoid in severe hepatic impairment	
Clomipramine	Avoid in severe hepatic impairment	Increased sedation
Cloxacillin	Use with caution	Cholestatic jaundice may occur up to several weeks after treatment has stopped. Risk increases with increasing age and if given for more than 2 weeks.
Codeine	Avoid or reduce dose	May precipitate coma. Causes constipation
Contraceptive, oral	Avoid in case of active liver disease	Avoid if history of cholestasis and pruritus during pregnancy.
Cyclophosphamide	Reduce dose	Monitor plasma level
Cyclosporine	Reduce dose and use with caution	Hepatotoxic
Cytarabine	Reduce dose	
Dacarbazine	Avoid in severe hepatic impairment	Dose reduction in mild to moderate hepatic impairment.
Daunorubicin	Reduce dose	Use with caution as toxicity increases in hepatic impairment.
Diazepam	Avoid in severe hepatic impairment.	Can precipitate coma
Didanosine	Monitor for toxicity	
Doxorubicin	Reduce dose according to bilirubin concentration	
Doxycycline	Avoid or use with caution	

Efavirenz	Avoid in severe hepatic impairment	Dose reduction and/or use with caution in mild to moderate hepatic impairment.
Enalapril	Use with caution	Closely monitor liver function in patients with hepatic impairment
Ergometrine	Avoid in severe hepatic impairment	
Erythromycin	Avoid in severe hepatic impairment	May cause idiosyncratic hepatotoxicity
Ethinylestradiol	Avoid	See also Contraceptives, Oral
Etoposide	Avoid in severe hepatic impairment	Increased risk of toxicity in case of hepatic impairment
Fluconazole	Use with caution	Hepatotoxicity
5-Fluorouracil	Use with caution; dose reduction may be required	
Fluoxetine	Reduce dose or administer on alternate days	
Fluphenazine	Avoid in severe hepatic impairment	Hepatotoxic, can precipitate coma
Furosemide	Avoid or use with caution in severe hepatic impairment	Hypokalaemia may precipitate coma (use potassium sparing diuretic to prevent this); Increased risk of hypomagnesaemia in alcoholic cirrhosis
Glibenclamide	Avoid or reduce the dose	Increased risk of hypoglycaemia. Can produce jaundice
Griseofulvin	Avoid in severe hepatic impairment	
Haloperidol	Use with caution	Can precipitate coma
Heparin	Reduce dose in severe liver disease	
Hydralazine	Reduce dose	
Hydrochlorothiazide	Avoid in severe hepatic impairment	Hypokalaemia may precipitate coma (use potassium sparing diuretic to prevent this); Increased risk of hypomagnesaemia in alcoholic cirrhosis

Ibuprofen	Avoid in severe hepatic impairment	Increased risk of gastrointestinal bleeding and can also cause fluid retention
Indinavir	Reduce dose to 600 mg 8th hly in mild to moderate hepatic impairment, not studied in severe hepatic impairment	
Isoniazid	Use with caution	Regularly monitor liver function and particularly frequently in first 2 months.
Levonorgestrel	Use with caution in active liver disease and recurrent cholestatic jaundice	
Lidocaine	Avoid or reduce the dose in severe hepatic impairment	
Magnesium hydroxide/sulphate	Avoid in hepatic coma if risk of renal failure	
Medroxyproges-terone	Avoid in active liver disease.	Avoid if history of pruritus and cholestasis during pregnancy
Mefloquine	Avoid for prophylaxis in severe liver disease	
6-Mercaptopurine	May need dose reduction	
Metformin	Avoid	Withdraw if tissue hypoxia likely
Methadone	Avoid or reduce the dose	May precipitate coma
Methotrexate	Avoid in severe hepatic impairment	Hepatotoxic, monitor liver functions
Methyldopa	Avoid in active liver disease	
Metoclopramide	Reduce dose	
Metronidazole	Reduce total daily dose to one third and give once daily in case of severe hepatic impairment	

Morphine	Avoid or reduce the dose	May precipitate coma
Nevirapine	Avoid in severe hepatic impairment	Use with caution in moderate hepatic impairment.
Nitrofurantoin	Use with caution	Cholestatic jaundice and chronic active hepatitis reported
Norethisterone	Avoid in active liver disease.	Avoid if history of pruritus and cholestasis during pregnancy
Ofloxacin	Reduce dose in severe hepatic impairment	Hepatic dysfunction reported
Paracetamol	Avoid large doses-dose related toxicity	
Phenobarbital	Avoid in severe hepatic impairment	May precipitate coma
Phenytoin	Reduce dose to avoid toxicity	
Prednisolone	Use with caution	Adverse effects more common
Procainamide	Avoid or reduce the dose	
Procarbazine	Avoid in severe hepatic impairment	
Promethazine	Avoid in severe hepatic impairment	May precipitate coma, Hepatotoxic
Propylthiouracil	Reduce dose	
Pyrazinamide	Avoid in severe hepatic impairment	Monitor hepatic function- idiosyncratic hepatotoxicity more common
Pyrimethamine	Use with caution	
Ranitidine	Reduce dose	Increased risk of confusion
Ribavirin	Avoid in severe hepatic impairment	
Rifampicin	Avoid or do not exceed 8 mg/kg daily	Monitor liver function

Saquinavir	Avoid in severe hepatic impairment. Caution in moderate hepatic impairment	
Simvastatin	Avoid in active liver disease or unexplained persistent elevation in serum transaminases	
Sodium nitroprusside	Avoid in severe hepatic impairment	
Sulfadiazine	Avoid in severe hepatic impairment	
Sulfamethoxazole + trimethoprim	Avoid in severe hepatic impairment	
Suxamethonium		Prolonged apnoea may occur in severe liver disease due to reduced hepatic synthesis of plasma cholinesterase
Testosterone	Preferably avoid	Possibility of dose related toxicity and fluid retention.
Thiopental	Reduce dose in severe liver disease	
Valproic acid	Avoid if possible	Hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months)
Verapamil	Reduce oral dose	
Vinblastine	Reduction of dose may require	
Vincristine	Reduction of dose may require	
Warfarin	Avoid in severe liver disease	Reduced production of clotting factors in hepatic impairment, may increase risk of bleeding
Zudovudine	Reduction of dose as accumulation may occur	

Appendix 7b: Lactation

Administration of some drugs (for example, ergotamine) to nursing mothers may harm the infant, whereas administration of others (for example, digoxin) has little effect. Some drugs inhibit lactation (for example, estrogens).

Toxicity to the infant can occur if the drug enters the milk in pharmacologically significant quantities. The concentration in milk of some drugs (for example, iodides) may exceed that in the maternal plasma so that therapeutic doses in the mother may cause toxicity to the infant. Some drugs inhibit the infant's sucking reflex (for example, phenobarbital). Drugs in breast milk may, at least theoretically, cause hypersensitivity in the infant even when the concentration is too low for a pharmacological effect.

The following table lists drugs:

- which should be used with caution or which are contraindicated in lactation for the reasons given above;
- which are not known to be harmful to the infant although they are present in milk in significant amounts.

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only drugs essential to a mother during lactation. Because of the inadequacy of information on drugs in breast milk the following table should be used only as a guide; absence from the table does not imply safety.

Drug	Comment
Abacavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Acetylsalicylic acid	Short course safe in usual dosage; monitor infant; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low; possible risk of Reye syndrome
Acyclovir	Significant amount in milk after systemic administration, but considered safe to use
Alcohol	Large amounts may affect infant and reduce milk consumption
Aminophylline	Present in milk-irritability in infant reported
Amitriptyline	Detectable in breast milk; continue lactation; adverse effects possible, monitor infant for drowsiness
Amoxycillin	Trace amounts in milk; safe in usual dosage; monitor infant
Amoxycillin + Clavulanic acid	Trace amounts in milk
Ampicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Artemether + Lumefantrine	Discontinue lactation during and for 1 week after stopping treatment; present in milk in *animal* studies
Asparaginase	Lactation contraindicated
Atenolol	Significant amounts in milk; safe in usual dosage; monitor infant
Atropine	Small amount present in milk; monitor infant
Azathioprine	Lactation contraindicated
Beclomethasone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses

Benzathine benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Betamethasone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Bleomycin	Lactation contraindicated
Carbamazepine	Continue lactation; adverse effects possible (severe skin reaction reported in 1 infant); monitor infant for drowsiness;
Ceftazidime	Excreted in low concentrations; safe in usual dosage; monitor infant
Ceftriaxone	Excreted in low concentrations; safe in usual dosage; monitor infant
Chlorambucil	Lactation contraindicated
Chloramphenicol	Continue lactation; use alternative drug if possible; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey syndrome'
Chlormethine	Lactation contraindicated
Chloroquine	For malaria prophylaxis, amount probably too small to be harmful; inadequate for reliable protection against malaria, ; avoid lactation when used for rheumatic disease
Chlorpheniramine	Safe in usual dosage; monitor infant for drowsiness
Chlorpromazine	Continue lactation; adverse effects possible; monitor infant for drowsiness
Ciprofloxacin	Continue lactation; use alternative drug if possible; high concentrations in breast milk
Cisplatin	Lactation contraindicated
Clindamycin	Amount probably too small to be harmful but bloody diarrhoea reported in 1 infant
Clomifene	May inhibit lactation

Clomipramine	Small amount present in milk; continue lactation; adverse effects possible; monitor infant for drowsiness
Clonazepam	Continue lactation; adverse effects possible; monitor infant for drowsiness;
Cloxacillin	Trace amounts in milk; safe in usual dosage; monitor infant
Colchicine	Present in milk but no adverse effects reported; caution because of risk of cytotoxicity
Contraceptives, oral	Combined oral contraceptives may inhibit lactation-use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (start 3 weeks after birth or later)
Cyclophosphamide	Lactation contraindicated during and for 36 h after stopping treatment
Cyclosporine	Present in milk-avoid
Cytarabine	Lactation contraindicated
Dacarbazine	Lactation contraindicated
Dactinomycin	Lactation contraindicated
Dapsone	Although significant amount in milk risk to infant very small; continue lactation; monitor infant for jaundice
Daunorubicin	Lactation contraindicated
Dexamethasone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Diazepam	Continue lactation; adverse effects possible; monitor infant for drowsiness;
Didanosine	Lactation recommended during first 6 months if no safe alternative to breast milk
Diloxanide	Avoid
Doxorubicin	Lactation contraindicated

Doxycycline	Continue lactation; use alternative drug if possible (absorption and therefore discolouration of teeth in infant probably usually prevented by chelation with calcium in milk)
Efavirenz	Lactation recommended during first 6 months if no safe alternative to breast milk
Eflornithine	Avoid
Ephedrine	Irritability and disturbed sleep reported
Ergocalciferol	Caution with high doses; may cause hypercalcaemia in infant
Ergotamine	Use alternative drug; ergotism may occur in infant; repeated doses may inhibit lactation
Erythromycin	Only small amounts in milk; safe in usual dosage; monitor infant
Ethinylestradiol	Use alternative method of contraception; may inhibit lactation; *see also* Contraceptives, Oral
Etoposide	Lactation contraindicated
Fluconazole	Present in milk; safe in usual dosage; monitor infant
Flucytosine	Avoid
5-Fluorouracil	Discontinue lactation
Fluphenazine	Amount excreted in milk probably too small to be harmful; continue lactation; adverse effects possible; monitor infant for drowsiness
Glibenclamide	Hypoglycaemia in infant
Haloperidol	Amount excreted in milk probably too small to be harmful; continue lactation; adverse effects possible; monitor infant for drowsiness
Halothane	Excreted in milk
Hydralazine	Present in milk but not known to be harmful; monitor infant
Hydrochlorothiazide	Use alternative drug; may inhibit lactation

Hydrocortisone	Systemic effects in infant unlikely with maternal dose of *less than equivalent* of prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Ibuprofen	Amount too small to be harmful; short courses safe in usual doses
Imipenem + Cilastatin	Present in milk-avoid
Indinavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Iodine	Stop lactation; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Isoniazid	Monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant
Ivermectin	Avoid treating mother until infant is 1week old
Lamivudine	Present in milk; lactation recommended during first 6 months if no safe alternative to breast milk
Levamisole	Lactation contraindicated
Levonorgestrel	Combined oral contraceptives may inhibit lactation-use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start 6 weeks after birth or later)
Lithium	Present in milk and risk of toxicity in infant; continue lactation; monitor infant carefully, particularly if risk of dehydration
Lopinavir + Ritonavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Lumefantrine	See Artemether + Lumefantrine
Medroxyprogesterone	Present in milk-no adverse effects reported (preferably start injectable contraceptive 6 weeks after birth or later)

Mefloquine	Present in milk but risk to infant minimal
6-Mercaptopurine	Lactation contraindicated
Metformin	Present in milk but safe in usual doses; monitor infant
Methotrexate	Lactation contraindicated
Metoclopramide	Present in milk; adverse effects possible; monitor infant for adverse effects
Metronidazole	Significant amount in milk; continue lactation; avoid large doses; use alternative drug if possible
Morphine	Short courses safe in usual doses; monitor infant
Nalidixic acid	Continue lactation; use alternative drug if possible; one case of haemolytic anaemia reported
Nelfinavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Neostigmine	Amount probably too small to be harmful; monitor infant
Nevirapine	Present in milk; lactation recommended during first 6 months if no safe alternative to breast milk
Nifedipine	Small amount in milk; continue lactation; monitor infant
Nitrofurantoin	Only small amounts in milk but could be enough to produce haemolysis in G-6-PD-deficient infants
Norethisterone	Combined oral contraceptives may inhibit lactation-use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start injectable contraceptive 6 weeks after birth or later)
Ofloxacin	Continue lactation; use alternative drug if possible
Paracetamol	Small amount present in milk: short courses safe in usual dosage; monitor infant
Pentamidine	Avoid unless essential

Pentavalent antimony compounds	Avoid
Phenobarbital	Continue lactation; adverse effects possible; monitor infant for drowsiness;
Phenoxymethylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Phenytoin	Small amount present in milk; continue lactation; adverse effects possible; monitor infant for drowsiness;
Potassium iodide	Stop lactation; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Povidone–iodine	Avoid; iodine absorbed from vaginal preparations is concentrated in milk
Praziquantel	Avoid lactation during and for 72 h after treatment; considered safe to continue lactation in treatment of schistosomiasis
Prednisolone	Systemic effects in infant unlikely with maternal dose of less than prednisolone 40 mg daily; monitor infant's adrenal function with higher doses
Primaquine	Avoid; risk of haemolysis in G-6-PD-deficient infants
Procainamide	Present in milk; continue lactation; monitor infant
Procarbazine	Lactation contraindicated
Promethazine	Safe in usual dosage; monitor infant for drowsiness
Propranolol	Present in milk; safe in usual dosage; monitor infant
Propylthiouracil	Monitor infant's thyroid status but amounts in milk probably too small to affect infant; high doses might affect neonatal thyroid function
Pyrimethamine	Significant amount-avoid administration of other folate antagonists to infant
Quinidine	Significant amount but not known to be harmful
Ranitidine	Significant amount present in milk, but not known to be harmful

Ritonavir	See Lopinavir with Ritonavir
Salbutamol	Safe in usual dosage; monitor infant
Saquinavir	Lactation recommended during first 6 months if no safe alternative to breast milk
Senna	Avoid; large doses may cause increased gastric motility and diarrhoea
Silver sulfadiazine	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G-6-PD-deficient infants
Sodium valproate	see Valproic acid
Stavudine	Lactation recommended during first 6 months if no safe alternative to breast milk
Sulfadiazine	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G-6-PD-deficient infants
Sulfadoxine + Pyrimethamine	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants and of haemolysis in G-6-PD-deficient infants (due to sulfadoxine)
Sulfamethoxazole + Trimethoprim	Continue lactation; monitor infant for jaundice-small risk of kernicterus in jaundiced infants and of haemolysis in G-6-PD-deficient infants (due to sulfamethoxazole)
Sulfasalazine	Continue lactation; monitor infant for jaundice-small amounts in milk (1 report of bloody diarrhoea and rashes); theoretical risk of neonatal haemolysis especially in G-6-PD-deficient infants
Tamoxifen	Suppresses lactation; avoid unless potential benefit outweighs risk
Testosterone	Avoid; may cause masculinization in the female infant or precocious development in the male infant; high doses suppress lactation

Tetracycline	Continue lactation; use alternative drug if possible (absorption and therefore discolouration of teeth in infant probably usually prevented by chelation with calcium in milk)
Theophylline	Present in milk-irritability in infant reported; modified-release preparations preferable
Thiamine	Severely thiamine-deficient mothers should avoid lactation as toxic methyl-glyoxal excreted in milk
Trimethoprim	Present in milk; safe in usual dosage; monitor infant
Valproic acid	Small amount present in milk; continue lactation; adverse effects possible; monitor infant for drowsiness; (Sodium valproate)
Vancomycin	Present in milk-significant absorption following oral administration unlikely
Vinblastine	Lactation contraindicated
Vincristine	Lactation contraindicated
Warfarin	Risk of haemorrhage; increased by vitamin-K deficiency; warfarin appears safe
Zidovudine	Lactation recommended during first 6 months if no safe alternative to breast milk

Appendix 7c: Pregnancy

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to remember this when prescribing for a woman of childbearing age. However, irrational fear of using drugs during pregnancy can also result in harm. This includes untreated illness, impaired maternal compliance, suboptimal treatment and treatment failures. Major congenital malformations occur in 2–4% of all live births, 15% of all diagnosed pregnancies will result in fetal loss. During the first trimester drugs may produce congenital malformations (teratogenesis), and the greater risk is from third to the eleventh week of pregnancy. During the second and third trimester, drugs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues. Drugs given shortly before term or during labor may have adverse effects on labor or on the neonate after delivery. Few drugs have been shown conclusively to be teratogenic in man but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

Prescribing in Pregnancy

Since, approximately 50% of pregnancies are unplanned and rest 50% are planned, if possible, counseling of women before a planned pregnancy should be carried out including discussion of risks associated with specific therapeutic agents, traditional drugs (alternative medicines), over the counter drugs and substances of abuse such as opioids, smoking, alcohol etc. Drugs should be prescribed in pregnancy only if the expected benefits to the mother are thought to be greater than the risk to the fetus. All drugs should be avoided if possible during the first trimester. Drugs which have been used extensively in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs and the smallest effective dose should be used. Keeping in view the prevalence of irrational polypharmacy, emphasis should be laid on promoting the use of well known single component drugs to multicomponent drugs. Since, there does appear to be an association of very potent topical corticosteroids with low birth weight, even the dermatological drug products being used should be cautiously selected and used.

The pronounced and progressive change in drug disposition that occurs during pregnancy is another major reason which calls for attention. Major physiological changes which influence drug disposition in mother and fetus are:

S. No	Physiologic changes	Effects
1.	Plasma albumin concentration of mother is reduced	Drug protein binding alteration
2.	Increased body fat in mother	Distribution of drug is effected
3.	Increased hepatic metabolism in mother	Faster hepatic clearance

4.	Increased cardiac output in mother	Increased renal blood flow and glomerular filtration and hence, increased elimination of drug
5.	Presence of placental barrier	Selectivity of drug permeation based on its hydrophobicity or molecular weight of drug
6.	Drug metabolizing enzymes activity in fetal liver is very low	Slow elimination of drugs by fetus

Though maternal medication carry the risk of increase in the incidence of abortion, stillbirths, fetal death, premature or delayed labor or create perinatal problems; but certain medications like folic acid are recommended for all pregnant women to reduce the rate of congenital anomalies specifically, the neural tube defect.
The Food and Drug Administration has categorized the drug risks to the fetus that runs from: "Category A" (safest) to "Category X" (known danger--do not use!)

Category A

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B

Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D

There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X

Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Appendix 7d: Renal Impairment

Dosing considerations in renal impairment

The number of patients with chronic kidney disease (CKD) and reduced renal function have been inexorably increasing. Reduced renal function may need adjustment in drug therapy as kidney plays a major role in the pharmacokinetics of a large number of drugs.

- Renal insufficiency frequently alters drug distribution volume. Edema and ascites increase the apparent volume of distribution of highly water-soluble or protein-bound drugs. Usual doses of such drugs given to edematous patients result in inadequate, low plasma levels.
- The alteration of plasma protein binding in patients with renal insufficiency is an important factor affecting both efficacy and toxicity. In patients with uremia the unbound fraction of several acidic drugs is substantially increased which may lead to serious toxicity.
- Although renal insufficiency is thought to affect primarily the renal elimination of drugs or metabolites, renal failure substantially affects drug biotransformation. Uremia slows the rate of reduction and hydrolysis reactions.
- Many active or toxic metabolites are produced during drug metabolism. Many of these metabolites depend on the kidneys for their removal from the body. The accumulation of active metabolites can explain in part the high incidence of ADRs seen in renal failure.

A few points should be kept in mind while prescribing;

- Renal function declines with age so that by the age of 80 it is half that in healthy young subjects.
- It is advisable to determine renal function not only before but also during the period of treatment and adjust the maintenance dose as necessary.
- One should try to keep drug prescription to minimum.
- Nephrotoxic drugs should, if possible, be avoided in all patients with renal disease because the nephrotoxicity is more likely to be serious.

- One should stay alert for unexpected ADRs.

The recommendations in the table below are meant only as a guide and do not imply efficacy or safety of a recommended dose in an individual patient.

A loading dose equivalent to the usual dose in patients with normal renal function should be considered for drugs with a particularly long half-life.

The table below gives the common drugs where in renal impairment dose adjustment is required.

When the dose method (D) is suggested, the percentage of the dose for normal renal function is given and when the interval method (I) is suggested, the actual dose interval is provided.

Drug	Dose Method	GFR >50 (ml/min)	GFR 10-50 (ml/min)	GFR <10 (ml/min)	CAPD	HD
Acetaminophen	I	q4h	q6h	q8h	Dose as GFR < 10	Dose as GFR < 10
Acetazolamide	I	q6h	q12h	Avoid	No data	No data
Acetylsalicyclic Acid	I	Q4h	Q4-6h	Avoid	As normal GFR	As normal GFR dose post HD
Acyclovir	D, I	5 mg/kg q8h	5 mg/kg q12-24h	2.5 mg/kg q24h	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Allopurinol	D	75%	50%	33%	Dose as GFR < 10	Dose as GFR < 10
Amikacin	D, I	60–90% q12h	30–70% q12–18h	20–30% q24–48h	15–20 mg /L/day	5 mg/kg post HD
Amiloride	D	100%	50%	Avoid	NA	NA
Aminophylline	D	100%	200–400 mg q12h	200–300 mg q12h	Dose as GFR < 10	Dose as GFR < 10
Amphotericin B	I	q24h	q24h	q24-36h	Dose as GFR < 10	Dose as GFR < 10
Ampicillin	I	q6h	q6–12h	q12-24h	Dose as GFR < 10	Dose as GFR < 10
Cefazolin	I	q8h	q12h	q24–48h	0.5 g q12h	0.5–1.0 g post HD

Cefixime	D	100%	75%	50%	200 mg q24h	200 mg q24h dose post HD
Cefotaxime	I	100% q8h	100% q8h	50% q8–12h	1 g q24h	Dose as GFR < 10 dose post HD
Chloroquine	D	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10
Ciprofloxacin	D	100%	50-75%	50%	250 mg q8h	250 mg q12h
Cisplatin	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Cyclophospha-mide	D	100%	75-100%	50-75%	Dose as GFR < 10	Dose as GFR < 10
Dapsone		100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10
Didanosine	I	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10
Digoxin	D, I	100% q24h	25–75% q36h	10–25% q48h	Dose as GFR < 10	Dose as GFR < 10
Enalapril	D	100%	75-100%	50-75%	Dose as GFR < 10	Dose as GFR < 10
Erythromycin	D	100%	100%	50-75%	Dose as GFR < 10	Dose as GFR < 10
Ethambutol	I	q24h	q24-36h	q48h	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Etoposide	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Fentanyl	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Fluconazole	D	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10 dose post HD

Gentamicin	D, I	60–90% q8–12h	30–70% q12h	20–30% q24–72h	3–4 mg/L/ day	Dose as GFR < 10 dose post HD
Isoniazid	D	100%	100%	75%	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Lamivudine	D, I	100%	50–150 mg qd	25 mg qd	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Metformin	D	50%	Avoid	Avoid	Avoid	Avoid
Metoclopra-mide	D	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10
Penicillin G	D	100%	75%	20-50%	Dose as GFR < 10	Dose as GFR < 10
Pyrazinamide	D	100%	As normal GFR	As normal GFR	As normal GFR	As normal GFR
Quinine	I	q8h	q8-12h	q24h	Dose as GFR < 10	Dose as GFR < 10 dose post HD
Streptomycin	I	q24h	q24–72h	q72h	20–40 mg /L/day	750 mg 2–3/ week
Triamterene	I	q12h	q12h	Avoid	Avoid	Avoid
Tubocurarine	D	75%	50%	Avoid	Unknown	Unknown
Vancomycin	D, I	500 mg q6-12h	500 mg q12-48h	500 mg q48-96h	Dose as GFR < 10	Dose as GFR < 10
Zidovudine (AZT)	D, I	100% q8h	100% q8h	50% q12h	Dose as GFR < 10	Dose as GFR < 10

HD: Hemodialysis; CAPD: Chronic Ambulatory Peritoneal Dialysis.

Appendix 13: Principles of Dose Calculation in Special Conditions

A. Dosing considerations for the pediatric patient

Determination of a safe and effective drug dose for the pediatric patient is essential for the treating physician. Doses and dosing intervals in children differ from that of an adult because of age-related variations in drug absorption, distribution, metabolism, and elimination. Oral drug absorption matures by four to five months of age. Drugs like phenytoin and chloramphenicol are absorbed slowly and erratically whereas penicillin and ampicillin are absorbed more efficiently than in the adults because of a higher gastric pH in the neonates. Most drug metabolizing enzymes are expressed at low levels at birth followed by postnatal induction of specific isoenzymes. For most drugs including phenytoin, barbiturates, digoxin and analgesics the plasma half lives are 2-3 times longer in neonates as compared to adults. Renal elimination of drugs is also reduced in the neonates. As a result, neonatal dosing regimens for a number of drugs must be reduced to avoid toxicity. Drug pharmacodynamics may also be different in children, for e.g. antihistamines and barbiturates that are generally sedative in adults may be excitatory in pediatric age group. Similarly, specific drug toxicities may be unique to this age group as evident in case of tetracyclines affecting teeth and glucocorticoids reducing linear growth of bones.

Because of these maturational differences in infants and children, simple proportionate reduction in the adult dose may not be adequate to determine an optimal pediatric dose. The most reliable dose information is usually the one provided by the drug manufacturer in the package insert or pediatric doses listed in the formulary. However, such information is not available for the majority of drugs since proper dose optimization studies are often not performed in the pediatric age range. Consequently, initial doses are derived by scaling down the dosages used in adults and then titrating according to clinical response.

In the absence of specific pediatric dose recommendations, an estimate can be made by any of several methods based on age, weight, or surface area.

Age- based rules:

Various rules of dosage in which the pediatric dose is a fraction of adult dose based on relative age have been used. Two of these are mentioned below.

Young's rule (for children 2 years and older)

$$\text{Child's dose (approx.)} = \frac{\text{Age (years)}}{\text{Age(years)} + 12} \times \text{Adult dose}$$

Fried's rule (for children up to 2 years old)

$$\text{Child's dose (approx.)} = \frac{\text{Age (months)}}{150} \times \text{Adult dose}$$

Weight based rule:

Because of large variability in weight among children of same age group, estimation of drug dosage for children on the basis of body weight is considered more reliable than that based solely on age. A rule proposed by Professor A. J. Clark (known as the Clark's rule) introduced weight proportional regimen for drug therapy.

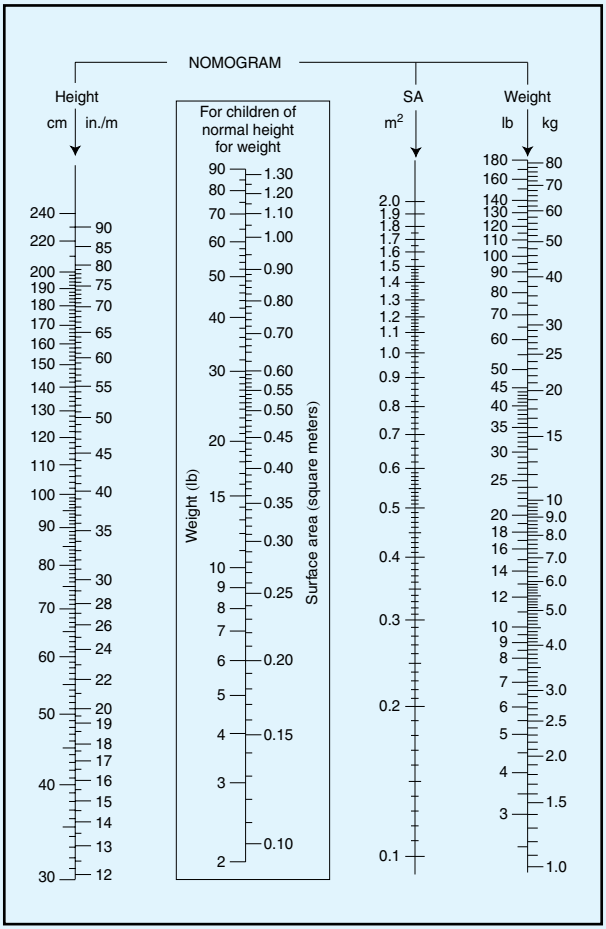
$$\text{Child's dose (approx.)} = \frac{\text{Weight (kg)}}{70} \times \text{Adult dose}$$

Body surface area based rule:

The most dependable methods for calculation of pediatric drug doses are those based on body surface area (BSA). Rate of metabolism and redistribution of drug, organ size, blood volume, extracellular fluid volume, renal blood flow and assays of blood concentration of drugs correlate closely with the BSA.

$$\text{Child's dose (approx.)} = \frac{\text{Weight (kg)}}{1.73\ m^2} \times \text{Adult dose}$$

For calculation of doses based on BSA, standard nomogram which includes both body weight and height as factors determining BSA should be used. To calculate a child's BSA, draw a straight line from the height column to the weight column. The point at which the line intersects the surface area (SA) column is the BSA (m^2). If the child is of roughly normal proportion, BSA can be calculated from the weight alone (in the enclosed area).



Note: This nomogram was published in Nelson Textbook of Pediatrics, 18th Edition, Richard E. Behrman, Robert M. Kliegman, MD, Hal B, Jenson, MD and Bonita F. Stanton, MD, Nomogram for the estimation of surface area, page no. 2951, fig no. 715-1, W. B. Saunders Company, 2007 and has been reproduced with permission.

The above mentioned rules are helpful in situations requiring the use of a drug that is unlicensed in children and for which no pediatric prescribing information is available. However, these rules are not precise and doses should not be calculated if it is possible to obtain the actual pediatric dose. Whatever be the method chosen to calculate the child's dose, it should never exceed that of the adult.

B. Dosing considerations for the geriatric patient

Aging is a natural process of human development and is characterized by a progressive loss of physiologic and reproductive functions. Altered response to drugs with aging occurs at both pharmacokinetic and pharmacodynamic levels.

Pharmacokinetic changes occur with the age as a result of the inevitable anatomical and physiological changes which occur with time, such as loss of an organ's functional units (nephrons, neurons) and distruption of some regulatory processes between cells and organs, resulting in decrease in function of body systems. For example, first pass metabolism decreases due to decrease in liver mass and blood flow, resulting in an increase in bioavailability of drugs which undergo extensive first pass metabolism, for example, propranolol. Another example of a pharmacokinetic change is the reduced clearance of renally-cleared drugs due to reduced renal plasma flow and glomerular filtration. This increases the potential for toxic effects particularly with those drugs where even marginal accumulation can have toxic effects, for example digoxin and lithium. Changes in body composition such as increase in body fat proportion and decrease in total body water result in a decreased volume of distribution for water soluble drugs such as digoxin, which increases their serum concentrations and potential for adverse effects.

Geriatric patients are much more "sensitive" to the action of many drugs, implying a change in the pharmacodynamic interactions of the drugs with their receptors. Elderly are more sensitive to some sedative-hypnotics and analgesics. Certain homeostatic control mechanisms appear to be blunted in elderly. Since homeostatic responses are often important components of the total response to a drug, these physiological alterations may change the pattern or intensity of drug response.

The age-related changes in the functions and composition of the human body require adjustments of drug selection and dosage for old individuals. Drug excretion via the kidneys declines with age, the elderly should therefore be treated as renally insufficient patients. A rough estimate of creatinine clearance can be obtained from the Cockcroft-Gault formula:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{Age}) \times (\text{Weight in kg})}{72 \times \text{serum creatinine in mg/dL}} \quad \text{(for males)}$$

For females, the result is multiplied by 0.85. The formula is applicable to patients between the age of 40 and 80.

The metabolic clearance is primarily reduced with drugs that display high hepatic extraction ('blood flow-limited metabolism'), whereas the metabolism of drugs with low hepatic extraction ('capacity-limited metabolism') usually is not diminished. Reduction of metabolic drug elimination is more pronounced in malnourished or frail subjects. The water content of the aging body decreases, the fat content rises, hence the distribution volume of hydrophilic compounds is reduced in the elderly, whereas that of lipophilic drugs is increased. Intestinal absorption of most drugs is not altered in the elderly. Aside of these pharmacokinetic changes, one of the characteristics of old age is a progressive decline in counterregulatory (homeostatic) mechanisms. Therefore drug effects are mitigated less, the reactions are usually stronger than in younger subjects, the rate and intensity of adverse effects are higher. Examples of drug effects augmented in this manner are, postural hypotension with agents that lower blood pressure, dehydration, hypovolemia, and electrolyte disturbances in response to diuretics, bleeding complications with oral anticoagulants, hypoglycemia with antidiabetics, and gastrointestinal irritation with non-steroidal anti-inflammatory drugs. The brain is an especially sensitive drug target in old age. Psychotropic drugs but also anticonvulsants and centrally acting antihypertensives may impede intellectual functions and motor coordination. The antimuscarinic effects of some antidepressants and neuroleptic drugs may be responsible for agitation, confusion, and delirium in elderly. Hence drugs should be used very restrictively in geriatric patients. If drug therapy is absolutely necessary, the dosage should be titrated to a clearly defined clinical or biochemical therapeutic goal starting from a low initial dose.

Appendix 14: Storage of Drugs

1. Definition and Concept

1.1. Storage

The term used to describe the safe keeping of all finished drugs and pharmaceuticals awaiting dispatch. The term is also applied for safe stores in hospitals and dispensaries under the specified conditions, so as to maintain their quality and potency.

1.2. Storage Conditions

The condition specified for storing the product e.g. temperature, humidity, container etc.

1.3. Quality

The ability of drug product to satisfy the users need.

1.4. Dosage Form

Refers to the gross physical form in which a drug is administered to or used by a patient.

1.5. Drug Product

A dosage form containing one or more active therapeutic ingredients along with other substance included during manufacturing process.

1.6. Finished Product

A medicinal product which has completed all stages of manufacture including packaging.

1.7. Strength

The concentration of the drug substance (for example weight/weight, weight/volume or unit dose/volume basis) and the potency i.e. the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example in terms of units by reference to a standard).

1.8. Stability

Degree of resistance to chemical and physical changes, the efficacy of the preparation must remain constant or change only within the limit specified by official compendia.

1.9. Expiration Date

The date placed on the immediate container label of a drug product that designates the date through which the product is expected to remain within specifications. Kinetically it is the

time required for 10 % of the material to disappear.

2. Storage Procedure and Instructions

Drugs must be stored under conditions which minimize deterioration, contamination or damage. They must be stored under conditions compatible with their recommended storage requirements of temperature and humidity and where necessary to comply with legal requirements, under secured or segregated conditions.

Appropriate storage conditions are:

Temperature or humidity controlled environment must be equipped with suitable indicators, recorders and/or failure warning devices which must be checked at appropriate intervals and the results are coded. Recording thermometers should be used. Temperature in uncontrolled storage products should also be monitored.

Temperature should be measured at different levels in the warehouse and if necessary storage of sensitive drugs should be restricted to locations in the warehouse where they will be protected from extreme conditions. Temperatures of the refrigerators, deep freezers, and Relative Humidity in humidity control area as well as general areas of storage at room temperature should be recorded on a daily basis.

Storage conditions not related to temperature are indicated in following terms:

Drug storage should be regularly checked for cleanliness and good order and for misplaced/deteriorated/out dated stock. All stocks should be checked regularly for obsolescence and degradation. Drugs with expired shelf life should be destroyed unless an extension of shelf life is granted following the satisfactory results or re-analysis. All due precautions should be observed to preclude issues of outdated Drugs.

Some categories of supplies require special storage conditions which include vaccines, narcotics, and combustibles e.g. vaccines require both refrigerator and freezers.

Narcotics and other controlled substances should be kept in secure locking rooms with only one entrance. The keys should be kept in a secure place, preferably a safe. Only the warehouse director and one another person should have access to them.

3. Inspection for Deterioration

Pharmacists should be aware that deterioration of drug product may happen even before their expiration. This may occur perhaps due to improper storage or the fact that the product may require critical storage conditions not stated on

the label. Hence inspection should include frequent product examination to detect signs of product deterioration which differ according to dosage form. Some examples, where deterioration may be physically detected are given here. The Pharmacists in the Stores should prepare an exhaustive list of following deterioration/spoilage indicators and keep them.

3.1. Liquid Dosage Forms

Slight gradual discolouration, Swirly precipitation, Whickering: pin hole at ampoule tip that leaks solution which precipitate or crystalline solid matter, clouding, fading of colour, Cake sedimentation (suspension), Creaming and cracking (emulsion), Discolouration.

3.2. Semisolid Dosage Forms

Ointments creams, gels and suppositories -Change in consistency and feel to touch, Phase separation, Discolouration, Surface crystal growth

3.3. Solid Dosage Forms

Surface chipping or pitting (plain tablets), Deformation (capsules), Increased hardness, Discolouration, Colour fading (coloured tablets), Chipping of coat (coated tablets).

Most vitamins, hormones enzymes are highly sensitive to oxidation and photo decomposition.

The integrity of packaging of dosage form is one of the important tasks of inspection for pharmacist as these protect the drug in a tailored fashion.

After each inspection, products showing any signs of instability should be subjected to sample analysis to ensure quality.

4. Drug Products Requiring Special Storage Conditions

4.1. Aerosols

Aerosols should be stored in a clean separate area away from heat and sunlight because the container contents are under pressure, filled containers must be checked for weight loss over the expiration dating period, for contents under pressure. The label should display "Do not expose to heat or store at a temperature above 40°C, keep out of reach of children".

4.2. Creams

Creams can be destroyed under extreme temperature fluctuations hence they should be stored at temperature above 10°C and not exceeding 30°C. If the creams are opened and diluted they should not be kept for more than 14 days to avoid microbial contamination.

4.3. Ophthalmic Solutions and Drops

They should be stored according to the conditions specified on the label. After opening they should not be used for more than one month at home and not more than 15 days in hospitals.

4.4. Capsules

Extremes of humidity and temperature should be avoided. High humidity (> 60% RH) at 21°C to 24°C produce more lasting effects. Capsules become softer, tackier and blotted. If temperature is increased the capsule shells may melt and fuse together. High temperature (>40°C) in dry place may cause cracking of capsule shell therefore capsules should be stored in air-conditioned area in which the humidity does not exceed 45% RH at 21 to 24°C.

4.5. Suppositories

Suppositories should be protected from heat and preferably stored in the refrigerator. Polyethylene glycol suppositories and suppositories enclosed in solid shell are less prone to distortion at temperature slightly above body temperature. Glycerinated gelatin suppositories should be protected from heat, moisture and dry air by packaging in well sealed containers and storing in a cold place.

4.6. Vaccines

Liquid vaccines are to be stored between 2° - 8°C and should not be frozen. All lyophilized vaccines should be stored between 2° - 8°C and for long term storage can be kept at or below -20°C or otherwise as specified in the individual monographs. Oral polio should be stored in a freezer -2° to -18°C.

5. Communicating the Prescription to the Patient

It is important that the drugs reach the patient in good and potent conditions and the patient should know and understand fully how to keep them till they are consumed. It is equally important that the patient should know the way each medicine is used. This will improve compliance and health outcome desired by the physician.

Communicating how and where to store the drugs to the Patient:

The following table may be used to guide and provide information on the way to store the drugs when they are dispensed to the patients. This is based on the recommended storage conditions as given on the labels of the drug products and Indian Pharmacopoeial notes in the General Chapters.

On the label	Meaning	Tell the Patient/ Representative of the Patient
Do not store over 8°C	To be stored in refrigerator (from +2°C to +8°C	Keep in the General Compartment of the refrigerator and do not keep in the place where you make Ice.
Do not store over 30 °C	To be stored at room temperature (from +2°C to +30°C)	Keep in any part of the house, except in Bath room/ Kitchen. Do not keep near or in the window area.
Do not freeze	To be kept in refrigerator (from +2°C to +8°C but not in the freezer chamber)	Keep in the General Compartment of the refrigerator and do not keep in the place where you make Ice.
Protect from moisture	To be stored in normal humidity at room temperature (RH less than 60%); to be provided by the manufacturer in a moisture-resistant container	The manufacturer would have provided such products in a moisture-resistant container/or packages. Keep in any part of the house, except in Bath room/Kitchen. Do not keep near or in the window area.

Protect from light	To be stored in a light-resistant cupboard/drawer; to be provided by the manufacturer in a light-resistant container.	The manufacturer would have provided such drug products in a light-resistant container/package. Keep in a cupboard/drawer or in a box with lid closed, in any part of the house, except in Bath room/Kitchen or near or in the window area.

Transit period care and Use of Cool Packs:

It is equally important to ensure that patients who carry drugs requiring special storage conditions like anti-cancer drugs, several types of insulins, vaccines, sera, toxoids, would need to carry them in cold conditions till they reach the place where they will keep for some time before usage or to another hospital/nursing home till it is administered. In such cases during transit they need to be packed in **"Thermo cool boxes with lid",** (#) with the drug product packs kept surrounded by adequate number of **"Cool Packs".**(#) "Cool Packs are available which come ready filled with such special liquid in sealed bags or plastic packs, which on keeping overnight in freezer compartment of a refrigerator becomes solid ice. Such packs help in keeping the drug products in the box retain temperatures below 8^{o}C for as much as 8 to 10 hours, which is generally adequate for transit protection. In case such cool packs are not available, it is recommended to use normal **"Hot cases"** (#) that people use to carry food, but stuffing the inside of the hot case boxes with sufficient ice cubes surrounding the drug packs kept inside, and the hot case suitably closed and sealed with sealing tapes. Cool packs can also be made by packing sufficient ice cubes into suitable sized self sealing polybags. (#) Several Pharmacists are known to innovate this way and they do serve for short transit times of up to one to two hours.

Appendix 15:
Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is defined as measurement of drug levels in the biological fluids usually blood (serum or plasma). It has been carried out in saliva, urine, sweat, tear fluids etc also. It is carried out for specific drugs at various time intervals in order to maintain a relatively constant concentration of the particular drug in the bloodstream and to optimize drug therapy. The main focus of TDM is on drugs with narrow therapeutic range. Apart from this, it also plays a significant role for drugs having large inter-individual variations; relatively toxic drugs used in concomitant disease conditions, for escalation of dose, drugs showing wide variation in their metabolism, major organ failure, poisoning cases, failure of therapeutic response, to enhance patient compliance, etc. It is very important in such situations in which the drugs are to be taken on chronic or life long basis (chronic disease conditions such as bipolar disorder, organ transplant rejection, neurological disorders etc.). The timing and frequency of blood collection after the medication and correct interpretation of results of analysis and their correlation with clinical features ensures the best therapeutic outcome.

Indications for drug monitoring:

- Drugs whose efficacy is difficult to establish clinically, like Phenytoin.
- Drugs with a narrow therapeutic index. Examples: Lithium, phenytoin, digoxin.
- Patients who have impaired clearance of a drug with a narrow therapeutic index. Example: Patients with renal failure have decreased clearance of digoxin and therefore are at a higher risk of toxicity.
- Drugs whose toxicity is difficult to distinguish from a patient's underlying disease. Example: Patients with chronic obstructive pulmonary disease treated with theophylline.

When not to do TDM

1. Drugs whose pharmacological effects can easily be used to dose titration, like oral hypoglycemic agents, anti-hypertensive drugs.
2. When easier and/or cheaper methods/alternatives to TDM are available to titrate the drug like International normalized ratio(INR) for warfarin.

Time of sample collection

1. Sample should be collected after steady state has been reached (5 half lives), unless TDM is intended to predict toxicity after single dose.
2. Usually "trough" concentrations are measured by taking the sample just before the subsequent dose.
3. Drugs whose half-lives are much shorter than the dosing interval, the peak and trough levels may be indicated to evaluate the dosage of drugs. Example: Gentamicin

TDM could be affected because of one or more of the factors relating to pharmacokinetics of the drug, or drug administration, or sample collection. Renal and hepatic alterations to half-life must also be considered. Laboratory variations also affect the TDM.

The folowing table summarizes the therapeutic concentration range of various drugs

Table: Important drugs requiring therapeutic monitoring

S. No	Pharmacological category	Drugs	Therapeutic drug conc. range
1.	Drugs acting on cardiovascular system	Amiodarone Digoxin Procainamide	1.0 - 2.5 µg/ml 0.8-2.0 ng/ml 4.0-10.0 µg/ml
2.	Antibiotics	Gentamycin Amikacin Vancomycin Tobramycin	5.0-10.0 µg/ml 15.0-25.0 µg/ml 15.0- 25.0 µg/ml 5.0-10.0 µg/ml
3.	Antiepileptics	Phenobarbital Phenytoin Valproic acid Carbamazepine Ethosuximide Gabapentin Lamotrigine	15.0-40.0 µg/ml 10.0-20.0 µg/ml 50.0-100.0 µg/ml 5.0-12.0 µg/ml 40.0-100.0 µg/ml 2.0-20.0 µg/ml 4.0-18.0 µg/ml
4.	Immunosuppressants	Cyclosporine Tacrolimus Sirolimus Mycophenolate mofetil	50.0-300.0 µg/ml 5.0-20.0 µg/l 5.0 – 15.0 µg/l 1.0- 60.0 mg/l
5.	Psychopharmacological agents	Lithium Imipramine Amitriptyline Nortriptyline Desipramine Clozapine	0.8-1.2 mEq/l 0.15- 0.3 µg/ml 0.12- 0.15 µg/ml 0.05-0.15 µg/ml 0.15- 0.3 µg/ml 0.35 to 0.6 mg/l
6.	Anti-infective	Cycloserine Ethambutol Pyrazinamide Streptomycin	20-35 µg/ml 2.0-6.0 µg/ml 20.0-50.0 µg/ml 35.0-45.0 µg/ml

TDM gives useful information regarding individual variations in drug utilization patterns as a consequence of altered physiological state or disease process and thus provides the clinician a better insight into the factors determining the patient's response to drug therapy.