

**Analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, drugs used to treat gout, and disease-modifying antirheumatic drugs**

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

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

### **Non-opioid analgesics**

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

### **Acetylsalicylic acid**

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

## **Acetylsalicylic acid**

*Tablets* , acetylsalicylic acid 300 mg

*Dispersible tablets* (Soluble tablets), acetylsalicylic acid 300 mg [not included on the WHO Model List]

*Suppositories* , acetylsalicylic acid 150 mg, 300 mg [300-mg strength not included on the WHO Model List]

### **Uses:**

mild to moderate pain including dysmenorrhoea, headache; pain and inflammation in rheumatic disease and other musculoskeletal disorders (including juvenile arthritis); pyrexia; acute migraine attack (section 7.1); antiplatelet (section 12.5)

### **Contraindications:**

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

### **Precautions:**

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

### **Dosage:**

Mild to moderate pain, pyrexia, *by mouth* with or after food, **ADULT** 300–900 mg every 4–6 hours if necessary; maximum 4 g daily; **CHILD** under 16 years not recommended

Mild to moderate pain, pyrexia, *by rectum* , **ADULT** 600–900 mg inserted every 4 hours if necessary; maximum 3.6 g daily; **CHILD** under 16 years not recommended

Inflammatory arthritis, *by mouth* with or after food, **ADULT** 4–8 g daily in divided doses in acute conditions; up to 5.4 g daily may be sufficient in chronic conditions

Juvenile arthritis, *by mouth* with or after food, **CHILD** up to 130 mg/kg daily in 5–6 divided doses in acute conditions; 80–100 mg/kg daily in divided doses for maintenance

### **Adverse effects:**

generally mild and infrequent for lower doses, but common with anti-inflammatory doses; gastrointestinal discomfort or nausea, ulceration with occult bleeding (occasionally major haemorrhage); also other haemorrhage (including

subconjunctival); hearing disturbances such as tinnitus (rarely deafness), vertigo, confusion, hypersensitivity reactions (angioedema, bronchospasm and rash); increased bleeding time; rarely oedema, myocarditis, blood disorders (particularly thrombocytopenia)

## **Paracetamol**

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

## **Paracetamol**

*Tablets* , paracetamol 500 mg

*Dispersible tablets* (Soluble tablets), paracetamol 120 mg, 500 mg [not included on WHO Model List]

*Oral solution* , paracetamol 120 mg/5 ml, 125 mg/5 ml, 250 mg/5 ml [120 mg/5 ml and 250 mg/5 ml strengths not included on WHO Model List]

*Suppositories* , paracetamol 60 mg, 100 mg, 125 mg, 250 mg, 500 mg [only 100-mg strength included on WHO Model List]

### **Uses:**

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

### **Precautions:**

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

### **Dosage:**

Post-immunization pyrexia, *by mouth* , **INFANT** 2–3 months, 60 mg followed by a second dose, if necessary, 4–6 hours later; warn parents to seek medical advice if pyrexia persists after second dose

Mild to moderate pain, pyrexia, *by mouth*, **ADULT** 0.5–1 g every 4–6 hours, maximum 4 g daily; **CHILD** under 3 months see note below, 3 months–1 year 60–125 mg, 1–5 years 120–250 mg, 6–12 years 250–500 mg, these doses may be repeated every 4–6 hours if necessary (maximum 4 doses in 24 hours)

Mild to moderate pain, pyrexia, *by rectum*, **ADULT** 0.5–1g; **CHILD** 1–5 years 125–250 mg, 6–12 years 250–500 mg; doses inserted every 4–6 hours if necessary, maximum 4 doses in 24 hours

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

#### **Adverse effects:**

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

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

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

Ibuprofen is used in the treatment of mild to moderate pain and in the management of pain and inflammation in rheumatoid arthritis and juvenile arthritis. It may also be of value in the less well-defined conditions of back pain and soft-tissue disorders. Ibuprofen is also used to reduce pain in children. With all NSAIDs caution should be exercised in the treatment of the elderly, in allergic disorders, during pregnancy and breastfeeding. In patients with renal, cardiac or hepatic impairment, the dose should be kept as low as possible and renal function should be monitored. NSAIDs should not be given to patients with active peptic ulceration and should preferably not be used in those with a history of the disease. The commonest adverse effects are generally gastrointestinal including nausea, vomiting, diarrhoea, and dyspepsia; hypersensitivity reactions including anaphylaxis, bronchospasm, and rash have been reported, as has fluid retention.

#### **Ibuprofen**

Tablets , ibuprofen 200 mg, 400 mg

**Uses:**

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

**Contraindications:**

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

**Precautions:**

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

**Dosage:**

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

Juvenile arthritis, *by mouth* with or after food, **CHILD** over 7 kg, 30–40 mg/kg daily in 3–4 divided doses

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

**Adverse effects:**

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

**Opioid analgesics**

Morphine is effective in relieving moderate to severe pain, particularly of visceral origin; there is a large variation in patient response. Weaker opioids such as codeine are suitable for mild to moderate pain.

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

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

### **Codeine phosphate**

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

*Tablets* , codeine phosphate, 30 mg

#### **Uses:**

mild to moderate pain; diarrhoea (section 17.7.2)

#### **Contraindications:**

respiratory depression, obstructive airways disease, acute asthma attack; where risk of paralytic ileus

#### **Precautions:**

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

#### **Dosage:**

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

#### **Adverse effects:**

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

## **Morphine salts**

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

*Tablets* , morphine sulfate 10 mg

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

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

### **Uses:**

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

### **Contraindications:**

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

### **Precautions:**

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

### **Dosage:**

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

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

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

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



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

**Adverse effects:**

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

**Drugs used in gout**

**Acute gout**

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

**Colchicine**

*Tablets* , colchicine 500 micrograms

**Uses:**

acute gout; short-term prophylaxis during initial therapy with allopurinol

**Contraindications:**

pregnancy (Appendix 2)

**Precautions:**

elderly; gastrointestinal disease; cardiac impairment; hepatic impairment; renal impairment (Appendix 4); breastfeeding (Appendix 3); **interactions:** Appendix 1

**Dosage:**

Acute gout, *by mouth* , **adult** 0.5–1 mg initially, followed by 500 micrograms every 2–3 hours until relief of pain is obtained, or vomiting or diarrhoea occurs; maximum total dose 6 mg; the course should not be repeated within 3 days

Prevention of gout attacks during initial treatment with allopurinol, **adult** 500 micrograms 2–3 times daily continuing for at least 1 month after hyperuricaemia has been corrected

**Adverse effects:**

nausea, vomiting, abdominal pain; excessive doses may cause severe diarrhoea, gastrointestinal haemorrhage, rash, renal and hepatic damage; rarely peripheral neuritis, myopathy, alopecia, inhibition of spermatogenesis; with prolonged treatment, blood disorders

**Chronic gout**

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

**Allopurinol**

*Tablets* , allopurinol 100 mg

**Uses:**

prophylaxis of gout; prophylaxis of hyperuricaemia associated with cancer chemotherapy

**Contraindications:**

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

**Precautions:**

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

**Dosage:**

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

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

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

**Adverse effects:**

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

**DMARDs (disease-modifying antirheumatic drugs)**

The process of cartilage and bone destruction which occurs in rheumatoid arthritis may be reduced by the use of a diverse group of drugs known as DMARDs (disease-modifying antirheumatic drugs). DMARDs include antimalarials (chloroquine, hydroxychloroquine), penicillamine, sulfasalazine, immunosuppressants (azathioprine, cyclophosphamide, methotrexate) and gold compounds.

Treatment should be started early in the course of the disease, before joint damage starts. Treatment is usually initiated with a NSAID when the diagnosis is uncertain and the disease course unpredictable. However, when the diagnosis, progression and severity of rheumatic disease have been confirmed, a DMARD should be introduced.

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

The antimalarial **chloroquine** is less effective than most other DMARDs, but as it is generally better tolerated it may be preferred in the treatment of mild rheumatoid arthritis. Chloroquine should not be used for psoriatic arthritis. Because long-term

therapy can result in retinopathy ophthalmological examinations should be conducted before and during treatment.

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

**Methotrexate**, an immunosuppressant, is considered to be a first-line DMARD; at the low doses used for rheumatoid arthritis it is well tolerated but there remains the risk of blood disorders (bone marrow suppression) and of hepatic and pulmonary toxicity. Other immunosuppressant drugs, including **azathioprine**, are generally reserved for use in patients with severe disease who have failed to respond to other DMARDs, especially in those with extra-cellular manifestations such as vasculitis. Immunosuppressants are used in psoriatic arthritis. Adverse reactions include blood disorders, alopecia, nausea and vomiting.

**Penicillamine** is not a first-line drug and its use is limited by a significant incidence of adverse effects including blood disorders (bone marrow suppression), proteinuria and rash.

**Corticosteroids** (section 18.1) are potent anti-inflammatory drugs but their place in the treatment of rheumatoid arthritis remains controversial. Their usefulness is limited by adverse effects and their use should be controlled by specialists. Corticosteroids are usually reserved for use in patients with severe disease which has failed to respond to other antirheumatic drugs, or where there are severe extra-articular effects such as vasculitis. Corticosteroids are also used to control disease activity during initial therapy with DMARDs. Although corticosteroids are associated with bone loss this appears to be dose-related; recent studies have suggested that a low dose of a corticosteroid started during the first two years of moderate to severe rheumatoid arthritis may reduce the rate of joint destruction. The smallest effective dose should be used, such as oral prednisolone 7.5 mg daily for 2–4 years only, and at the end of treatment the dose should be tapered off slowly to avoid possible long term adverse effects. Relatively high doses of a corticosteroid, with cyclophosphamide, may be needed to control vasculitis.

## **Azathioprine**

Azathioprine is a complementary drug for rheumatoid arthritis

*Tablets*, azathioprine 50 mg

### **Uses:**

rheumatoid arthritis in cases that have failed to respond to chloroquine or penicillamine; psoriatic arthritis; transplant rejection (section 8.1); inflammatory bowel disease (section 17.4)

### **Contraindications:**

hypersensitivity to azathioprine or mercaptopurine

**Precautions:**

monitor throughout treatment including blood counts; hepatic impairment (Appendix 5); renal impairment (Appendix 4); elderly (reduce dose); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

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

**Dosage:**

Administered on expert advice

Rheumatoid arthritis, *by mouth* , initially, 1.5–2.5 mg/kg daily in divided doses, adjusted according to response; maintenance 1–3 mg/kg daily; consider withdrawal if no improvement within 3 months

**Adverse effects:**

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

**Chloroquine salts**

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

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

**Uses:**

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

**Contraindications:**

psoriatic arthritis

**Precautions:**

monitor visual acuity throughout treatment; warn patient to report immediately any unexplained visual disturbances; hepatic impairment; renal impairment (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); neurological disorders including

epilepsy; severe gastrointestinal disorders; G6PD deficiency; elderly; may exacerbate psoriasis and aggravate myasthenia gravis; porphyria; **interactions:** Appendix 1

### **Dosage:**

Administered on expert advice

*Note.* All doses in terms of chloroquine base

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

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

### **Adverse effects:**

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

### **Methotrexate**

Methotrexate is a complementary drug for rheumatoid arthritis

*Tablets* , methotrexate 2.5 mg

### **Uses:**

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

### **Contraindications:**

pregnancy and breastfeeding (Appendices 2 and 3); immunodeficiency syndromes; significant pleural effusion or ascites

### **Precautions:**

monitor throughout treatment including blood counts and hepatic and renal function tests; renal and hepatic impairment (avoid if severe, see also Appendices 4 and 5); reduce dose or withdraw if acute infection develops; for woman or man, contraception during and for at least 6 months after treatment; peptic ulceration, ulcerative colitis, diarrhoea, ulcerative stomatitis; advise patient to avoid self-medication with

salicylates or other NSAIDs; warn patient with rheumatoid arthritis to report cough or dyspnoea; **interactions:** Appendix 1

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

### **Dosage:**

Administered on expert advice

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

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

### **Adverse effects:**

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

## **Penicillamine**

Penicillamine is a complementary drug for rheumatoid arthritis

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

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

### **Uses:**

severe rheumatoid arthritis; copper and lead poisoning (section 4.2.5)

### **Contraindications:**

hypersensitivity; lupus erythematosus

### **Precautions:**

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

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

### **Dosage:**

Administered on expert advice

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

### **Adverse effects:**

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

### **Sulfasalazine**

Sulfasalazine is a complementary drug for rheumatoid arthritis

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

### **Uses:**

severe rheumatoid arthritis; ulcerative colitis and Crohn disease (section 17.4)

### **Contraindications:**

hypersensitivity to salicylates and sulfonamides; severe renal impairment; child under 2 years; porphyria

### **Precautions:**

monitor during first 3 months of treatment including blood counts and hepatic and renal function tests; renal impairment (Appendix 4); pregnancy and breastfeeding



(Appendices 2 and 3); history of allergy; G6PD deficiency; slow acetylator status;  
**interactions:** Appendix 1

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

**Dosage:**

Administered on expert advice

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

**Adverse effects:**

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