PRODUCT INFORMATION

QUINBISUL
quinine bisulfate

NAME OF THE MEDICINE:
The active ingredient of QUINBISUL is quinine bisulfate.

Quinine bisulfate is the heptahydrate of (8S,9R)-6-methoxycinchonan-9-ol hydrogen sulfate. Its structural formula is:

Molecular formula: C_{20}H_{24}N_2O_2.H_2SO_4.7H_2O
Molecular weight: 548.6
CAS Registry No.: 549-56-4 (anhydrous)

DESCRIPTION:
Quinine bisulfate appears as colourless crystals or a white, crystalline powder; odourless. Efflorescent in dry air. It is soluble in 8 parts of water and in 50 parts of ethanol (96%).

Each QUINBISUL tablet contains 300 mg of quinine bisulphate. It also contains the following inactive excipients: lactose, cellulose-microcrystalline, povidone, talc-purified, sodium starch glycollate, starch-pregelatinised maize, silica-colloidal anhydrous, magnesium stearate, carnauba wax and opadry white OY-LS-28908 (PI).

PHARMACOLOGY:
Antimalarial action. Quinine is not a true causal prophylactic agent; it is incapable of preventing sporozoite-induced vivax or falciparum malaria in human volunteers. However, it is effective as a suppressive drug and in the control of overt clinical attacks. Its primary action is schizonticidal, and no lethal effect is exerted on sporozoites or pre-erythrocytic tissue forms. In addition, quinine is gametocytocidal for \textit{P. vivax} and \textit{P. malariae} but not for \textit{P. falciparum}. The exact mechanism of quinine’s antimalarial action is uncertain. Quinine can form a hydrogen-bonded complex with double stranded DNA which inhibits protein synthesis by preventing strand separation and therefore DNA replication and transcription to RNA.

Central nervous system. Quinine has slight analgesic and antipyretic activity. Quinine has indifferent results on fevers, other than malarial fever, indicating that it is not a potent antipyretic, and it is rarely used for this purpose. Quinine resembles the salicylates in its analgesic properties, especially in joint and muscle pain. It acts centrally, but is ineffective against severe pain.

Cardiovascular system. The actions of quinine on cardiac muscle are qualitatively similar to those of its isomer quinidine. Therapeutic doses of quinine have little if any effect on the normal cardiovascular system in man.

Smooth muscle. Quinine has little effect on smooth muscle other than a slight oxytocic action on the gravid uterus, especially during the third trimester of pregnancy. The spleen may contract as a
result of the direct action of quinine on the musculature of its capsule, thus producing a lymphocytosis sometimes observed after therapeutic doses of the drug.

**Skeletal muscle.** Quinine increases the tension response to a single maximal stimulus delivered to the muscle directly or through the nerve, but it increases the refractory period of muscle so that the response to tetanic stimulus is diminished. Quinine also decreases the excitability of the motor end-plate region so that the responses to repetitive nerve stimulation and to acetylcholine are reduced. Thus it has a curare-like effect on skeletal muscle.

**Other actions.** Quinine has strong prostaglandin antagonistic action and weak agonistic activity. The antagonistic effect is clearly demonstrable at concentrations attained therapeutically. Quinine has slight local anaesthetic activity. The anaesthesia may last for many hours or days.

**Pharmacokinetics**

**Absorption.** Quinine bisulfate is readily and almost completely absorbed from the gastrointestinal tract, even in patients with marked diarrhoea. Absorption occurs mainly from the upper small intestine and peak plasma concentrations are achieved 1 to 3 hours after ingestion. For example, after single doses of 4 mg/kg in aqueous solution peak plasma concentrations of 1.1 and 2.4 micrograms/mL were achieved in young and old adults, respectively. After chronic administration of total daily doses of 1 g of quinine, the average plasma quinine concentration is approximately 7 micrograms/mL.

**Distribution.** Quinine is widely distributed into body tissues. Only 2 to 5% of the plasma quinine concentration is found in the CSF, probably as a result of the extent of binding to plasma proteins. Quinine readily crosses the placenta and has been found in the tissues of the foetus. The apparent volume of distribution has been found to vary with age and dose. For example, in the case of young and elderly subjects receiving oral doses of 4 mg/kg the apparent volumes of distribution were 3.2 and 1.7 litres/kg respectively. In another study, the apparent volumes of distribution following doses of 100, 325 and 650 mg three times daily for three days were 38.6, 58.1 and 85.8 litres respectively.

**Protein binding.** Approximately 70% of quinine is bound to plasma proteins.

**Metabolism.** Metabolism of quinine occurs largely in the liver, with less than 5% of unaltered drug excreted in the urine. Metabolism occurs largely by hydroxylation, principally to a 2-hydroxyquinoline derivative and a 6-hydroxyquinuclidine derivative, both of which show little antimalarial activity. In a study of quinine disposition during malaria and experimentally induced fever it was found that in all subjects plasma levels of quinine, and the ratio of plasma quinine to plasma metabolites, were increased during malaria, suggesting impaired hepatic metabolism of quinine. A similar observation was noted for changes in quinine metabolism during artificially induced fever.

**Excretion.** After termination of therapy, plasma levels fall rapidly and only negligible concentrations of quinine are present after 24 hours. Less than 5% of quinine is excreted in the urine, and renal excretion is twice as rapid in acid urine as in alkaline urine. Renal excretion of quinine is limited by the binding of a large fraction to plasma proteins.

**Half-life.** In one study a dose-dependent prolongation of plasma quinine half-life was observed. After doses of 100, 325 and 650 mg three times daily for three days, measurements of plasma half-lives were 8.5, 12.4, and 16.4 hours respectively. In another study 5 subjects were given 540 mg of quinine base every 8 hours until a total of 9 doses had been administered. The average plasma half-life values before malaria and during malaria were found to be 7.3 and 8.3 hours respectively.

**Clinical implications of pharmacokinetic data.** Quinine bisulfate is readily absorbed after oral administration. Volume of distribution is dose-dependent. Protein binding is 70%. Clearance is principally by hepatic metabolism. Plasma half-life is about 8 hours, increasing with dosage.
INDICATIONS:

Treatment of malaria due to strains of *P. falciparum* resistant to chloroquine and the related 4-aminoquinolines.

CONTRAINDICATIONS:

Quinbisul should not be used in patients hypersensitive to quinine, in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or in patients with a history of blackwater fever.

Since thrombocytopenia, which may be fatal, and haemolytic uraemic syndrome with acute renal failure may follow the administration of quinine in highly sensitive patients, a history of this occurrence associated with previous quinine ingestion contraindicates its further use. Recovery usually occurs following withdrawal of the medication and appropriate therapy.

Myasthenia gravis (see ADVERSE EFFECTS); tinnitus; optic neuritis.

PRECAUTIONS:

*Hypersensitivity.* Hypersensitivity reactions, including cutaneous flushing, pruritus, rash (urticarial, papular, scarlatinial), fever, facial oedema, gastrointestinal distress, dyspnoea, tinnitus and impairment of vision have been reported with quinine. Extreme flushing of the skin with intense, generalised pruritus is the most frequently reported hypersensitivity reaction to the drug. Haemoglobinuria and asthma have also been reported rarely. If evidence of hypersensitivity occurs during quinine therapy, the drug should be discontinued.

*Haemolysis.* Haemolysis, with the potential for haemolytic anaemia, has been reported when quinine was administered to patients with G-6-PD deficiency. Quinine should be stopped immediately if haemolysis occurs and supportive measures instituted.

*Prothrombin formation.* Quinine is capable of causing hypoprothrombinaemia (i.e. depresses the formation of prothrombin) and may enhance the effects of anticoagulants. The simultaneous administration of vitamin K counteracts the prolongation of the prothrombin time.

*Atrial fibrillation.* Patients with atrial fibrillation should be digitalised before receiving quinine, because quinine may otherwise cause an increase in the ventricular rate.

Use in Pregnancy (Category: D)

The use of antimalarials in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus. Prophylaxis in high risk situations is also justified.

In toxic doses, quinine causes foetal damage in the form of deafness, development disturbances and malformations of the extremities and cranium in both animals and humans. Its ability to induce uterine contractions also constitutes a risk of abortion.

Use in Lactation

Caution should be exercised when quinine is given to nursing mothers because quinine is excreted in small amounts in breast milk.

Interactions with other medicines

*Quinine-containing beverages.* Excessive quantities of quinine-containing beverages should not be consumed while taking quinine as this may increase the risk of adverse reactions and toxicity.
**Pyrimethamine.** Pyrimethamine may displace quinine from plasma protein binding sites resulting in excessive free quinine, and perhaps quinine toxicity.

**Digoxin/digitoxin.** Increased plasma levels of digoxin have been demonstrated in individuals after concomitant quinine administration. Increased plasma levels of digitoxin have been demonstrated in individuals after concomitant quinidine administration. It is therefore recommended that plasma levels of digoxin or digitoxin be determined periodically for those individuals taking either of these glycosides and quinine concomitantly.

**Antacids.** Concurrent use of aluminium-containing antacids may delay or decrease absorption of quinine.

**Anticoagulants.** Cinchona alkaloids, including quinine, have the potential to depress the hepatic enzyme system that synthesises the vitamin K-dependent factors. The resulting hypoprothrombinaemic effect may enhance the action of warfarin and other oral anticoagulants.

**Neuromuscular blocking agents.** The effects of neuromuscular blocking agents (particularly pancuronium, succinylcholine and tubocurarine) may be potentiated with quinine, and result in respiratory difficulties.

**Acidifiers and alkalinisers.** Ammonium chloride and other drugs which may lower the pH of the urine (urinary acidifiers) considerably increases the renal excretion of quinine. Conversely, urinary alkalinisers (such as acetazolamide and sodium bicarbonate) may increase quinine blood levels with potential for toxicity.

**Mefloquine.** Because adverse cardiac effects may be additive, mefloquine should not be used concomitantly with quinine. Concomitant use of mefloquine and quinine may result in ECG abnormalities or cardiac arrest and may increase the risk of seizures.

**Cimetidine.** Cimetidine has been reported to reduce the clearance and prolong the elimination half-life of quinine following concomitant oral administration of the drugs in healthy adults. The clinical significance of this interaction is not known.

**Potential interaction. Skeletal muscle relaxants.** In view of the known effect of quinine in patients with myasthenia gravis (see ADVERSE EFFECTS), it may potentiate the effect of both depolarising and nondepolarising muscle relaxants.

**Effects on laboratory tests**

Quinine may produce an elevated value for urinary 17-ketogenic steroids when the Zimmerman method is used.

**ADVERSE EFFECTS:**

When quinine is given repeatedly in full doses, a typical group of symptoms occurs to which the term cinchonism has been applied. Cinchonism has certain features in common with salicylate poisoning. Mildest forms consist of tinnitus, headache, nausea, and slightly disturbed vision. If the medication is continued or in overdose, symptoms also involve the gastrointestinal tract, the central nervous and cardiovascular systems, and the skin. In some individuals, small doses of quinine cause toxic manifestations.

The following adverse reactions have been reported with quinine in therapeutic or excessive dosage (individual or multiple symptoms may represent cinchonism or hypersensitivity).

**Haematological.** Acute haemolysis, thrombocytopenic purpura, agranulocytosis, hypoprothrombinaemia.
Central nervous system. Visual disturbances including blurred vision with scotomata, photophobia, diplopia, mydriasis, constricted visual fields, night blindness and disturbed colour perception. Visual disturbances are generally reversible following discontinuation of the drug, but in severe cases, optic atrophy may result. Tinnitus, deafness and vertigo. Headache, fever, apprehension, restlessness, confusion and syncope.

Dermatological/allergic. Cutaneous rashes (urticarial, the most frequent type of allergic reaction, papular or scarlatinal), pruritus, flushing of the skin, sweating, occasional oedema of the face.

Respiratory. Asthmatic symptoms.

Cardiovascular. Disturbances in cardiac rhythm or conduction, widening of the QRS complex, hypotension, ventricular tachycardia and anginal symptoms have occurred with prolonged quinine therapy in highly sensitive patients.

Gastrointestinal. Nausea and vomiting (may be CNS related), epigastric pain.

Musculoskeletal. Quinine decreases neuromuscular transmission by increasing the threshold of excitability at the myoneural junction, and depresses the muscle action potential. It may therefore aggravate the symptoms of patients with myasthenia gravis.

Hepatic. Hepatitis.

Renal. Anuria, uraemia, haemoglobinuria.

Serious or life-threatening reactions. Quinine can cause thrombocytopenia which may be fatal. There have been reports of haemolytic uraemic syndrome with acute renal failure following a single 300 mg dose of quinine. Acute haemolytic anaemia is rare and normally disappears on withdrawal of the drug.

DOSAGE AND ADMINISTRATION:

Adults. The typical oral dose of quinine in the treatment of chloroquine-resistant *P. falciparum* malaria is 600 mg three times daily after meals for 7 to 14 days, plus 75 mg pyrimethamine/1,500 mg sulfadoxine as a single dose on the second day of treatment.

In certain emergencies such as cerebral malaria, quinine should be given by intravenous injection or infusion. The dihydrochloride is employed and the injection should be made very slowly, preferably by IV infusion. The optimal daily dose is 10 to 20 mg/kg, usually given as two separate infusions over four hours each. Quinine bisulfate is unsuitable for use in injections since its solution decomposes on heating.

Therapeutic range of serum levels: 2 to 5 microgram/mL.

Paediatric. For the treatment of chloroquine resistant malaria in children, administer 10 mg/kg quinine three times daily for 7 to 10 days, in combination with an appropriate single dose of pyrimethamine/sulfadoxine.

Geriatric. A study of the pharmacokinetics of quinine in elderly (older than 65 years) and young (20 to 40 years) subjects indicated that a significantly higher peak plasma concentration was achieved in the elderly subjects following a standard oral dose of quinine sulfate. This is probably influenced by the decrease in plasma clearance observed in the elderly patients. In view of this it may be necessary to reduce the normal adult dosage.
OVERDOSAGE:

The most common signs and symptoms of overdosage are tinnitus, dizziness, skin rash and gastrointestinal disturbances (intestinal cramping). With higher doses, cardiovascular and CNS effects may occur, including headache, fever, vomiting, apprehension, confusion and convulsions. Other effects are listed in the ADVERSE EFFECTS section.

Fatalities have been reported from a single dose of 2-8 g of quinine and a single fatality reported with a 1.5 g dose (which may reflect an idiosyncratic effect). Several cases of blindness following large overdoses of quinine, with partial recovery of vision in each instance, have been reported. Tinnitus and impaired hearing may occur at plasma quinine concentrations over 10 microgram/mL. This level would not be normally attained with the dose of 1-2 quinine tablets daily, but in hypersensitive patients, as little as 0.3 g of quinine may produce tinnitus.

Treatment of overdose with QUINBISUL should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient together with careful monitoring of ECG, respiratory status and central nervous system toxicity. There is no specific antidote for overdose with QUINBISUL. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug.

Patients should be warned of possible blindness but reassured that some recovery of sight frequently occurs. Stellate block has also been used effectively for quinine-associated blindness. Residual visual impairment occasionally yields to vasodilators.

Contact the Poisons Information Centre on 131126 for management of overdose.

PRESENTATION AND STORAGE CONDITIONS:

White film coated, unscored, convex tablet marked “QB 300” on one side and “G” on the other side.

Bottles of 30* and 50 tablets. (*30 tablets currently not available in Australia)

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR:

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos St
St Leonards NSW 2065
Australia

POISON SCHEDULE OF THE MEDICINE:

S4

DATE OF APPROVAL:

Approved by the Therapeutic Goods Administration: 19 January 2005
Date of most recent amendment: 5 August 2010.