PRODUCT INFORMATION

QUINATE®
Quinine sulfate

NAME OF THE MEDICINE

QUINATE (quinine sulfate).

DESCRIPTION

Quinine sulfate is the sulfate of an alkaloid obtained from the bark of species of Cinchona. It contains not less that 99.0 per cent and not more that 101.0 per cent of total alkaloid salt, calculated as \( \text{C}_{20}\text{H}_{24}\text{N}_{2}\text{O}_{2} \cdot \text{H}_{2}\text{SO}_{4} \), on the anhydrous basis. It is a white or almost white or colourless, fine, crystalline solid. Quinine sulfate dihydrate has the following structural formula:

\[
\text{H}_2\text{CO} \vl{1} \text{H} \vl{2} \text{N} \vl{3} \text{H} \vl{4} \text{O} \vl{5} \text{H} \vl{6} \text{N} \vl{7} \text{H} \vl{8} \text{CH}_2 \vl{9} \text{H} \vl{10} \text{H} \vl{11} \text{C}_2\text{H}_2\text{N}_2\text{O}_2 \vl{12} \text{H}_2\text{SO}_4 \vl{13} \text{H}_2\text{O} \vl{14}
\]

Molecular weight: 783.0. CAS Registry Number: 6119-70-6.

QUINATE tablets contain 300 mg of quinine sulfate. They also contain the excipients lactose monohydrate, maize starch, povidone, sodium starch glycollate, magnesium stearate and Opadry complete film coating system White Y-1-7000.

PHARMACOLOGY

Quinine affects a large variety of biological systems. From the therapeutic viewpoint, the following are most relevant.

Central nervous system. Quinine exerts a slight antipyretic effect, and an analgesic action resembling that of the salicylate group, especially on joint and muscle pain. Although Quinine acts centrally, it is ineffective against severe pain.

Cardiovascular system. Quinine acts in a similar qualitative manner on cardiac muscle as does its isomer quinidine, the anti-arrhythmic drug. However, therapeutic doses of quinine have little or no effect on the normal cardiovascular system in man.

Smooth muscle. Quinine has a mild stimulatory effect on the pregnant uterus which is an oxytocic stimulation. It also passes the placental barrier. Quinine may also cause the smooth muscle in the spleen to contract producing lymphocytosis, sometimes observed after therapeutic doses of the drug.

Skeletal muscle. Quinine has a dual action in skeletal muscle: it acts directly on the muscle fibre increases the tension response, and also increases the refractory period; it affects neuromuscular transmission by increasing the threshold of excitability of the motor endplate.

Antimalarial Action. Quinine is also effective in malaria. Although the exact mechanism of action is not known, Quinine appears to interfere with plasmoidal DNA.
*Other actions.* Quinine has a strong prostaglandin antagonistic action and a weak agonistic activity. The antagonistic effect is clearly demonstrated at concentrations attained therapeutically. Quinine has a slight local anaesthetic activity. The anaesthesia may last for many hours or days.

**PHARMACOKINETICS**

**Absorption**
Absorption occurs readily when given orally, and occurs mainly in the upper small intestine. Plasma concentrations after single oral doses are approximately the same as after comparable intravenous doses. Peak plasma concentrations occur within 1-3 hours after a single oral dose. Quinine sulfate is 70% bound to plasma proteins.

**Metabolism**
Metabolism occurs largely in the liver, with less than 5% excreted unaltered in the urine.

**Elimination**
After cessation of quinine therapy, the plasma level falls rapidly, and only a negligible concentration is present after 24 hours. No accumulation in body tissues occurs with continued administration. The inactive metabolites are excreted mainly in the urine.

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

**CONTRAINDICATIONS**
- Patients hypersensitive to quinine and patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.
- 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 or in patients with a history of blackwater fever.

**PRECAUTIONS**

**Haemolysis.** 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.

**Hypersensitivity reactions.** Hypersensitivity reactions, including cutaneous flushing, pruritus, rash (urticarial, papular, scarlatinial), fever, facial oedems, 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.

**Use in Pregnancy** is Category D. The use of antimalarials in the treatment of life-threatening malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus. Prophylaxis in high risk situation is also justified.

In high doses, quinine causes foetal injuries 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 breast milk (in small amounts).

INTERACTIONS WITH OTHER MEDICINES

- 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.
- Concurrent use of aluminium containing antacids may delay or decrease absorption of quinine.
- 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 anticoagulants.
- Excessive quantities of quinine-containing beverages should not be consumed while taking quinine as this may increase the risk of adverse reactions and toxicity.
- The effects of neuromuscular blocking agents (particularly pancuronium, succinylcholine and tubocurarine) may be potentiated with quinine, and result in respiratory difficulties.
- Concomitant use of quinine and mefloquine may produce additive effects and may result in ECG abnormalities or cardiac arrest and may increase the risk of seizures.
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- Cimetidine has been reported to decrease the clearance and prolong the elimination half-life of quinine following concomitant use in healthy adults. The clinical significance of this interaction is unknown.
- In view of the known effects of quinine in patients with myasthenia gravis it may potentiate the effect of both depolarising and non-depolarising muscle relaxants.
- Urinary alkalinisers (such as acetazolamide and sodium bicarbonate) may increase quinine blood levels with potential for toxicity.
- Prothrombin formation may be prolonged and the effects of anticoagulants may be enhanced (see also Precautions section).

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

ADVERSE EFFECTS

Cinchonism is the term given to a group of symptoms which usually occurs when quinine is given repeatedly in full doses. 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 involve the gastrointestinal tract, CNS and CVS 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 doses. (individual or multiple symptoms may represent cinchonism or hypersensitivity.)

- **Haematological.** Acute haemolysis, thrombocytopenic purpura, agranulocytosis, hypoprothrombinaemia.
- **CNS.** Visual disturbances, including blurred vision with scotomata, photophobia, diplopia, diminished visual fields and distorted colour vision. Although visual disturbances are generally reversible following discontinuation of the drug, in severe cases, optic atrophy may result. Tinnitus, deafness and vertigo. Headache, nausea, vomiting, 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.** Anginal symptoms, conduction disturbances, ventricular tachycardia, widening of the QRS complex and anginal symptoms have occurred with prolonged therapy in highly sensitive patients.
- **Gastrointestinal.** Nausea and vomiting (may be CNS related), epigastric pain, hepatitis.
- **Renal.** Anuria, uraemia and haemoglobinuria.
Quinine can cause thrombocytopenia which may be fatal. There have been reports of haemolytic uraemic syndrome and acute renal failure following a single dose of 300 mg of quinine. Acute haemolytic anaemia is rare and normally disappears on discontinuation of the drug.

**DOSAGE AND ADMINISTRATION**

**Adults:** quinine sulfate 600 mg (adult <50 kg: 450 mg) orally after a meal, 8 hourly for 7 to 14 days and Pyrimethamine 75 mg + sulfadoxine 1500 mg as a single dose on the second day of the treatment.

**Children:** quinine sulfate 10 mg/kg body weight (up to 600 mg) orally, 8 hourly for 7 to 10 days, in combination with appropriate single dose of Pyrimethamine/sulfadoxine.

**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. Abortion, low blood pressure and renal failure are also possible results of overdosage. 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 concentration of over 10 microgram/mL. This level would not be normally attained with the dose of 1-2 quinine tablets a day, but in hypersensitive patients, as little as 0.3 g of quinine may produce tinnitus.

**Treatment** for overdosage with QUINATE 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 QUINATE. 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 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, round, biconvex film coated tablet. Available in HDPE bottles of 50.

Store below 30 °C.

**POISONS SCHEDULE**

S4

**NAME AND ADDRESS OF THE SPONSOR**

Arrow Pharma Pty Ltd
15 – 17 Chapel Street
Cremorne VIC 3121

**DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)**

20 January 2004
DATE OF MOST RECENT AMENDMENT

4 July 2017