

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Quinine Bisulphate Tablets 300mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinine Bisulphate 300.00 mg BP

3 PHARMACEUTICAL FORM

Coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of:- chloroquine-resistant malaria. Treatment and prevention of nocturnal leg cramps in adults and the elderly, when cramps cause regular disruption of sleep (see section 4.2 and Section 4.4)

4.2 Posology and method of administration

Route of administration: Oral

For malaria:

Adults: in the treatment of chloroquine-resistant malaria - 600mg at 8 hourly intervals for 7 days.

Children: 10mg per kg bodyweight at 8 hourly intervals for 7 days

For the treatment and prevention of nocturnal leg cramps:

Adults (including elderly):

The recommended dose is 300mg at bedtime.

A reduction in frequency of leg cramps may take up to 4 weeks to become apparent. Patients should be monitored closely during the early stages of

treatment for adverse effects. After an initial trial of 4 weeks, treatment should be stopped if there is no benefit. Treatment should be interrupted at approximately three monthly intervals to reassess the benefit of treatment.

Children: Not recommended

4.3 Contraindications

In patients with a history of hypersensitivity to quinine or any of the excipients in the tablet. In the presence of haemoglobinuria during malaria. Optic neuritis.

Tinnitus

Myasthenia gravis.

4.4 Special warnings and precautions for use

Use with caution in patients with atrial fibrillation or other serious heart disease. It may cause hypoprothrombinaemia. May cause severe respiratory distress, dysphagia in patients with myasthenia gravis. Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency may develop acute haemolytic anaemia. Monitor treatment in all patients in case signs of resistance develop. Renal impairment which may be due to an immune mechanism may occur. Hypoglycaemia may occur.

Administration of quinine may give rise to cinchonism, which is generally more severe in overdose, but may also occur in normal therapeutic doses. Patients should be warned not to exceed the prescribed dose, because of the possibility of serious, irreversible side effects in overdose. Treatment for night cramps should be stopped if symptoms of cinchonism emerge. Such symptoms include tinnitus, impaired hearing, headache, nausea, and disturbed vision (see sections 4.8 and 4.9).

Hypersensitivity to quinine may also occur with symptoms of cinchonism together with urticaria, flushing, pruritus, rash, fever, angioedema, dyspnoea and asthma.

Before use for nocturnal leg cramps, the risks, which include significant adverse effects and interactions (see sections 4.5 and 4.8), should be carefully considered relative to the potential benefits. These risks are likely to be of particular concern in the elderly. Quinine should only be considered when cramps are very painful or frequent, when other treatable causes of cramp have been ruled out, and when non-pharmacological measures have not worked. Quinine sulphate should not be used for this indication during pregnancy (see Section 4.6).

Quinine may cause unpredictable serious and life-threatening thrombocytopenia, which is thought to be an idiosyncratic hypersensitivity

reaction. Quinine should not be prescribed or administered to patients who have previously experienced any adverse reaction to quinine, including that in tonic water or other beverages. Patients should be instructed to stop treatment and consult a physician if signs of thrombocytopenia such as unexplained bruising or bleeding occur.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on quinine

Quinine is metabolised via hepatic oxidative cytochrome P450 pathways, predominantly by CYP3A4. There is the potential for increased quinine toxicity with concurrent use of potent CYP3A4 inhibitors, which include azole antifungal drugs and HIV protease inhibitors.

Sub-optimal quinine serum levels may result from concomitant use of CYP3A4 inducers, which include rifampicin, barbiturates, carbamazepine and phenytoin.

Care should be taken when quinine is used in combination with other CYP3A4 substrates, especially those causing prolongation of the QT interval. Cimetidine inhibits metabolism (plasma quinine concentration increases).

Effect of quinine on other drugs

Plasma concentration of Flecainide and mefloquine is increased.

Quinine interacts with digoxin producing raised serum digoxin level.

Quinine can decrease plasma concentrations of ciclosporin.

Other drug interactions

There is an increased risk of ventricular arrhythmias with other drugs which prolong the QT interval, including amiodarone, moxifloxacin, pimozide, thioridazine and halofantrine.

Concurrent use with oral hypoglycaemics may increase the risk of hypoglycaemia .

Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants.

Quinine enhances the neuromuscular effects of suxamethonium.

Concomitant use of quinidine may increase the possibility of cinchonism.

Chloroquine and quinine appear to be antagonistic when given together for *P falciparum* malaria.

4.6 Pregnancy and lactation

Pregnancy

Quinine may cause congenital abnormalities of the CNS and extremities. Following administration of large doses during pregnancy, phototoxicity and deafness have been reported in neonates. Quinine sulphate should not be used during pregnancy unless the benefits outweigh the risks.

Treatment of chloroquine-resistant strains of falciparum malaria. Pregnancy in a patient with malaria is not generally regarded as a contra-indication to the use of quinine. As malaria infection is potentially serious during pregnancy and poses a threat to the mother and foetus, there appears to be little justification in withholding treatment in the absence of a suitable alternative.

Prophylaxis of nocturnal leg-cramps.

Quinine sulphate should not be used during pregnancy to treat cramps.

Lactation

Quinine sulphate is excreted in breast milk, but no problems in humans have been reported. However, quinine sulphate should not be given to nursing mothers unless the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

Quinine may cause visual disturbances and vertigo, hence patients should be advised that if affected they should not drive or operate machinery.

4.8 Undesirable effects

Some patients are hypersensitive to quinine bisulphate and they may experience the symptoms of cinchonism together with asthma and other allergic manifestations including angioneurotic oedema and haemolytic anaemia.

Cinchonism is more common in overdose, but may occur even after normal doses of quinine. In its mild form symptoms include tinnitus, impaired hearing, rashes, headache, nausea and disturbed vision. Its more severe manifestations symptoms may include gastrointestinal symptoms, oculotoxicity, CNS disturbances, cardiotoxicity and death (see section 4.9). Visual disorders may include blurred vision, defective colour perception, visual field constriction and total blindness.

MedDRA system organ class	Adverse Reaction
Blood and lymphatic system disorders	Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolytic-uremic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura
Immune system disorders	Generalised hypersensitivity reactions including angioneurotic oedema and fever
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Agitation, confusion
Nervous system disorders	Headache, vertigo
Eye disorders	Blurred vision, defective colour perception, visual field constriction
Ear and labyrinth disorders	Tinnitus, impaired hearing
Cardiac disorders	Atrioventricular conduction disturbances, hypotension, prolongation of the QT interval, widening of the QRS complex and T wave flattening
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritis, photosensitivity
Musculoskeletal and connective tissue disorders	Muscle weakness, aggravation of myasthenia gravis
Renal and urinary disorders	Renal insufficiency, acute renal failure

4.9 Overdose

Symptoms

Quinine overdosage may lead to serious and irreversible side effects and can be fatal. In acute overdosage, symptoms of cinchonism may occur, including convulsions, nausea, vomiting, tinnitus, deafness, headache, vasodilation and disturbed vision.

Features of a significant overdose include convulsions, impairment of consciousness, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. Hypokalaemia and hypoglycaemia may also occur.

Fatalities have been reported in adults after doses of 2-8g. High doses of quinine are teratogenic and may cause miscarriage.

Treatment:

Children (< 5 years) who have ingested any amount should be referred to hospital. Older children and adults should be referred to hospital if more than 30 mg/kg of quinine base has been taken. Quinine bisulphate 300mg tablet is equivalent to 178 mg quinine base.

Quinine is rapidly absorbed.

Consider activated charcoal (50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of more than 30 mg/kg quinine base or any amount in a child under 5 years. Multiple dose activated charcoal will enhance quinine elimination.

Observe patients for at least 12 hours after ingestion. Monitor cardiac conduction and rhythm, serum electrolytes, blood glucose and visual acuity.

Other treatment is mostly symptomatic to maintain blood pressure, respiration, renal function and to treat arrhythmia, convulsions, hypoglycaemia and acidosis. .

Elimination from the body may be assisted by the acidification of the urine with ammonium chloride. Haemodialysis and haemoperfusion should be instituted but this has limited value because quinine is extensively metabolised in the liver and only a small proportion is excreted unchanged in the urine. Signs of haemolytic anaemia may be indicative of a need to treat acute renal failure. Respiratory failure may be combatted by assisted respiration. Cardiac rhythm should be monitored. Vasodilators such as nicotinic acid and amylnitrite may be given in an attempt to reverse visual impairment. Beneficial effects have been achieved with stellate ganglion block. The average fatal dose in adults has been reported to be with 8g, with death resulting in a few hours or delayed for 1-2 days. Large doses can induce abortion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Quinine is a highly active blood schizonticide and suppresses the asexual cycle of development of malaria parasites in the erythrocytes. It is considered to act by interfering with DNA.

5.2 Pharmacokinetic properties

Quinine is almost completely absorbed from the gastro-intestinal tract. Peak concentrations in the circulation is attained about 1-3 hours after ingestion and about 70% is bound to proteins in the plasma. Quinine is readily diffused across the placenta. It is degraded in the body, mainly in the liver, and only a small proportion is excreted in the urine unchanged.

The plasma half-life is 11 hours.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Fumed silicon dioxide
Guar gum
Magnesium stearate
Hydroxypropylmethylcellulose
Ethylcellulose
Titanium dioxide

Diethylphthalate
Beeswax
Methanol
Petroleum spirit
Dichloromethane

6.2 Incompatibilities

None known

6.3 Shelf life

48 months all sizes

6.4 Special precautions for storage

Store in a well closed container. Store in a dry place below 25°

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polythene lids and polyurethane or polythene inserts

16, 21, 28, 30, 50, 56, 60, 84, 90, 100 tablets.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
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Croydon, Surrey, CR0 0XT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0428

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

9th January 1998

10 DATE OF REVISION OF THE TEXT

27/05/ 2010

11 DOSIMETRY (IF APPLICABLE)

**12 INSTRUCTIONS FOR PREPARATION OF
RADIOPHARMACEUTICALS (IF APPLICABLE)**