SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Quinine Sulphate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinine Sulphate 300.00 mg BP

3 PHARMACEUTICAL FORM

Coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Quinine is a highly active blood schizonticide and suppresses the asexual cycle of development of malaria parasites in the erythrocytes. It is now mainly used in the treatment of *P falciparum* malaria resistant to other antimalarial drugs.
2. 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

1. For malaria:

Adults: 600 mg of quinine sulphate every 8 hours for 7 days

Elderly: as for adults

Children: 10 mg/kg every 8 hours for 7 days

2. For the treatment and prevention of nocturnal leg cramps:

Adults (including elderly):
The recommended dose is 200mg at bedtime. The maximum dose is 300mg.

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

Route of administration: oral

4.3 Contraindications

Quinine is contra-indicated in patients with:
Hypersensitivity to quinine or to any of the excipient in the tablet
Haemoglobinuria during malaria
Tinnitus
Myasthenia gravis
Optic neuritis.

4.4 Special warnings and precautions for use

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.

Quinine should be used with caution in patients with atrial fibrillation or other serious heart disease. It may cause hypoprothrombinaemia.

Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency may develop acute haemolytic anaemia.

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 section 4.8 and 4.9).

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

Patients with rare hereditary problems of fructose intolerance, glucose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Monitor treatment in all patients in case signs of resistance develop.

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.

Effect of quinine on other drugs

The plasma concentration of flecainide, digoxin and mefloquine may be increased.

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 benefit outweigh the risk (e.g. when the mother is treated for Malignant Tertian Malone).
Treatment of chloroquine-resistant strains of falciparium 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

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 side effects including irreversible visual loss, and can be fatal.
Symptoms include vomiting, tinnitus, deafness, headache, and visual disturbance.

Features of a significant overdose include convulsions, impairment of consciousness, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. High doses of quinine are tetrogenic and may cause miscarriage. Hypokalaemia and hypoglycaemia may also occur.

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.

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

Note: each 300mg tablet is equivalent to 248 mg quinine base.

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

Starch
Sucrose
PVP
Sodium starch glycollate
Talc
Magnesium stearate
Purified water

In the coating:
Hydroxypropyl methylcellulose 15cps
Hydroxypropyl methylcellulose 5cps
Ethylcellulose
Diethylphthalate
Titanium dioxide
Saccharin Sodium
Beeswax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36months all sizes

6.4 Special precautions for storage

Store below 25°C in a dry place.

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 in packs of 100, 250 and 500.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/10/2005

10 DATE OF REVISION OF THE TEXT

28/07/2010