SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Quinine Sulfate 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Quinine Sulfate 200mg
Excipient with known effect: Also contain sodium methyl, ethyl and propyl parahydroxybenzoates (E215, E217, E219)
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
White, sugar coated deep convex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Quinine sulfate tablets are indicated for the following:
1. Treatment of Falciparum (malignant tertian) malaria.
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

Posology

Treatment of malaria
Adults and Children over 12 years: 600mg quinine sulphate every 8 hours
Children: 10mg/kg bodyweight every 8 hours
Not suitable for children under 1 year.
These doses are usually given for 7 days and, if quinine resistance is known or suspected, then treatment should be followed with an appropriate course of pyrimethamine/sulfadoxine or doxycycline.
Use in the elderly: Dosage as for adults.

Nocturnal leg cramps
Adults and Children over 12 years: 200 - 300mg quinine sulphate at bedtime
Use in the elderly: Dosage as for adults.

**Method of Administration**
For oral administration.

### 4.3 Contraindications
- Hypersensitivity to quinine or any of the other ingredients
- Haemoglobinuria
- Optic neuritis
- Tinnitus
- Myasthenia gravis, quinine may cause severe respiratory distress and dysphagia in these patients.

### 4.4 Special warnings and precautions for use

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

#### Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency
- The administration of quinine to a patient who has previously been suffering from a chronic and inadequately controlled malarial infection may precipitate an attack of blackwater fever. However, in some cases deficiency of glucose-6-phosphate dehydrogenase may have been involved. Glucose-6-phosphate dehydrogenase deficient patients with malaria or taking quinine to treat leg cramps may be at an increased risk of haemolytic anaemia during quinine therapy.
- Quinine should not be withheld from pregnant women who have life threatening malaria (see section 4.6).
- Treatment with quinine should be monitored in case signs of resistance develop.
- 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 sulfate 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.

- Reduce the dosage (or increase intervals between doses) in renal or hepatic disease.

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

### 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.

- **Ciclosporin:** Quinine can decrease plasma concentrations of ciclosporin.
- **Amantadine:** Quinine can reduce the renal clearance of amantadine.
- **Cardiac glycosides:** Quinine increases plasma concentrations of cardiac glycosides and reduced dosage of concomitant cardiac glycosides such as digoxin to half the maintenance dose may be necessary.

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

- **Hypoglycaemics:** Concurrent use with oral hypoglycaemics may increase the risk of hypoglycaemia.

- **Anticoagulants:** Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants.

- **Suxamethonium:** Quinine enhances the neuromuscular effects of suxamethonium.
Antiarrhythmics: Concomitant use of amiodarone should be avoided due to the increased risk of ventricular arrhythmias. The plasma concentration of flecainide is increased by quinine. Concomitant use of quinidine may increase the possibility of cinchonism.

Antimalarials: According to the manufacturer of artemether with lumefantrine concomitant use should be avoided. There is an increased risk of convulsions when given with mefloquine. Chloroquine and quinine appear to be antagonistic when given together for P falciparum malaria. There is a decrease in plasma concentrations of primaquine.

Antibacterials: There is an increased risk of ventricular arrhythmias when moxifloxacin is given with quinine. Rifampicin can reduced the serum levels of quinine, therefore reducing its therapeutic effect.

Antihistamines: Concomitant use of terfenadine should be avoided due to the increased risk of ventricular arrhythmias.

Antipsychotics: There is an increased risk of ventricular arrhythmias and concomitant use should be avoided with pimozide or thioridazine.

Ulcer-healing drugs: Cimetidine inhibits quinine metabolism leading to increased plasma-quinine concentrations.

4.6 Fertility, 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 sulfate should not be used during pregnancy unless the benefits outweigh the risks.

Treatment 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 sulfate should not be used during pregnancy to treat cramps.

Lactation
Quinine sulfate is excreted in breast milk, but no problems in humans have been reported. However, quinine sulfate 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

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinchonism</td>
<td>It 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.</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolytic-uremic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Reports have been received of eczematous dermatitis, oedema, erythema and lichen planus. Hypersensitivity reactions including asthma, angioneurotic oedema, photosensitivity, hot and flushed skin, pruritis, thrombocytopenic purpura, urticarial and fever</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia may occur after oral administration although it is more common after parenteral administration.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation, confusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, vertigo, excitement, loss of consciousness, coma and death</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Blurred vision, defective colour perception, visual field constriction</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus, impaired hearing</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Atrioventricular conduction disturbances, hypotension, prolongation of the QT interval, widening of the QRS complex and T wave flattening</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm, dyspnoea may occur.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, diarrhoea, abdominal pain may occur after long term administration of quinine.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritis,</td>
</tr>
</tbody>
</table>
disorders | photosensitivity
---|---
Musculoskeletal and connective tissue disorders | Muscle weakness, aggravation of myasthenia gravis
Renal and urinary disorders | Renal insufficiency, acute renal failure may be due to an immune mechanism or to circulatory failure.
*Reproductive system and breast disorders* | Toxic doses of quinine may induce abortion, but it is unwise to withhold the drug if less toxic antimalarials are not available

**Reporting of Suspected adverse reactions:**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

**Symptoms**
Quinine overdosage may lead to serious side effects including irreversible visual loss, and can be fatal. In acute overdosage, 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. Fatalities have been reported in adults after doses of 2-8g. High doses of quinine are teratogenic 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 30mg/kg of quinine base has been taken.
Each 200mg Quinine sulfate tablet is equivalent to 165mg quinine base, each 300mg Quinine sulfate tablet is equivalent to 248mg quinine base.

Quinine is rapidly absorbed. Consider activated charcoal (50g for adults; 1g/kg for children) if the patient presents within 1 hour of ingestion of more than 30mg/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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: P01B C01, Quinine alkaloid.

Quinine is a cinchona alkaloid and a 4-methanolquinoline antimalarial agent which is a rapidly acting blood schizontocide with activity against *Plasmodium falciparum, P vivax, P ovale* and *P malariae*. It is active against the gametocytes of *P malariae* and *P vivax*, but not against mature gametocytes of *P falciparum*. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias.

Quinine has effects on the motor end-plate of skeletal muscle and prolongs the refractory period. Like quinidine, quinine is a sodium channel blocker and, therefore, has local anaesthetic, and both anti- and proarrhythmic activity.

The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite.

5.2 Pharmacokinetic properties

The pharmacokinetics of quinine are altered significantly by malaria infection, the major effects being reductions in both its apparent volume of distribution and its clearance.

Absorption: Quinine is rapidly and almost completely absorbed from the gastrointestinal tract. and peak concentration in the circulation is attained about 1 to 3 hours after oral administration of the sulfate.

Distribution: Plasma protein binding is about 70 % in healthy subjects and rises to 90% or more in patients with malaria.

Quinine is widely distributed throughout the body. Concentrations attained in the CSF of patients with cerebral malaria have been reported to be about 2-7% of those in the plasma.

Metabolism: Quinine is extensively metabolised in the liver and rapidly excreted mainly in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5% to 20%. The pharmacokinetics of quinine are altered significant by malaria infection, with reductions in both apparent volume of distribution and clearance.

Elimination: Excretion is increased in acid urine. The elimination half-life is about 11 hours in healthy subjects but may be prolonged in patients with malaria. Small amounts of quinine also appear in the bile and saliva.

Quinine crosses the placenta and is excreted in the breast milk.
5.3 **Preclinical safety data**
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
- Powdered cellulose
- Stearic acid
- Magnesium stearate
- Talc
- Anhydrous colloidal silica
- Sodium starch glycollate
- Dextrin
- Gelatin
- Titanium dioxide (E171)
- Sucrose
- Sodium methyl, ethyl and propyl parahydroxybenzoates (E215, E217, E219)

6.2 **Incompatibilities**
None known

6.3 **Shelf life**
5 years for opaque plastic containers
2 years for blisters

6.4 **Special precautions for storage**
Protect from heat, light and moisture

6.5 **Nature and contents of container**
1. Opaque plastic containers with plastic caps in pack sizes of 28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000.
2. Opaque plastic container composed of either high density polypropylene or high density polyethylene with a tamper evident or child resistant tamper evident closure composed of high density polyethylene for all pack sizes (28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000) packaging inclusion: polyether foam or polyethylene or polypropylene made filler.

3. Blister packs of aluminium/opaque PVC subsequently packed in printed cartons in pack sizes of 28, 42, 56, 84 and 112.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special instructions

7 MARKETING AUTHORITY
Bristol Laboratories Limited
Unit 3, Canalside,
Northbridge road,
Berkhamsted HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0515

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
15/07/2016