SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Quinine Sulfate Tablets BP 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 300 mg of Quinine Sulfate.
Excipients of known effect: Also contains 34mg of lactose and 156mg of sucrose.
For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM
Tablet
White, bi-convex, sugar coated tablets

4. CLINICAL PARTICULARS
4.1. Therapeutic Indications
1) For the treatment of Plasmodium 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:

For the treatment of falciparum (malignant tertian) malaria
**Adults (including the elderly) and children aged 12 years and over:** Two tablets (600 mg) to be taken every 8 hours for a period of 7 days. The dose may depend upon the size of the patient, severity of infection, and evidence of renal or liver disease (when the intervals should be increased), due to a prolonged half-life of the drug.

If quinine resistance is known or suspected on completion of the course additional treatment may be given. This may be one of the following:

1. doxycycline 200mg daily (as a single dose or in 2 divided doses) for at least 7 days.
2. clindamycin 300mg four times daily for 5 days.

**Children under 12 years of age:** Dosage is dependant on bodyweight as follows- 10 mg/kg to be taken every 8 hours for a period of 7 days.

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.

**Method of Administration:**

For oral administration

4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- Optic neuritis,
- Tinnitus
- Haemoglobinuria.
- 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.

Cardiac disorders

- Caution is required if administered to patients with atrial fibrillation, heart block, other cardiac conduction defects, or other serious heart disease. It may cause hypoprothrombinemia and enhance the effects of anticoagulants.

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 black water 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 are at 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 all patients 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 in 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

**Important information regarding the ingredients of this medicine**

This medicinal product contains sucrose and lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

### 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.

**Other drugs interactions**

Amantadine: Quinine can reduce the renal clearance of amantadine with risk of amantadine toxicity (including headache, nausea, dizziness).

Analgesics: increased risk of ventricular arrhythmias with levacetylmethadol (avoid concomitant use).

Ciclosporin: Quinine can decrease serum plasma concentrations of ciclosporin.

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.
Anti-arrhythmics: 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.

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

Hypoglycaemics: Concurrent use with oral hypoglycaemias may increase the risk of hypoglycaemia.

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

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

Antimalarials: There may be an increased risk of side effects if quinine is used with other antimalarials, for example, chloroquine, halofantrine and mefloquine (increased risk of convulsions), although this should not prevent their use in severe cases. Quinine may increase the plasma concentration of mefloquine. Chloroquine and quinine appear to be antagonistic when given together for P falciparum malaria. There is an increased risk of ventricular arrhythmias with halofantrine.

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

Suxamethonium: Quinine enhances the neuromuscular effects of suxamethonium.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Large doses of quinine can induce abortion. Congenital malformations of the optic and auditory nerves have been reported after quinine has failed to induce abortion. 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.

**Breast-feeding**

Quinine sulfate is excreted in breast milk, but no problems in humans have been reported. Infants at risk for glucose-6-phosphate dehydrogenase deficiency should not be breast-fed until this disease can be ruled out. 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**

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 manifestation 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

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorder</td>
<td>Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolytic-uremic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura</td>
</tr>
<tr>
<td>MedDRA system organ class</td>
<td>Adverse Reaction</td>
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<tr>
<td>------------------------------------------------</td>
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<tr>
<td>Immune system disorders</td>
<td>Eczematous dermatitis, oedema, erythema and lichen planus, hypersensitivity reactions including angioneurotic oedema, asthma, photosensitivity, hot and flushed skin, pruritus, thrombocytopenic purpura, urticarial and fever have also been reported.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia may occur after oral 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 coupled with a feeble pulse, prolongation of the QT interval, widening of the QRS complex and T wave flattening has been noted with therapeutic doses.</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 disorders</td>
<td>Flushing, rash, urticaria, eczematous, dermatitis, oedema, erythema, lichen planus, pruritus, photosensitivity</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle weakness, aggravation of myasthenia gravis</td>
</tr>
<tr>
<td>MedDRA system organ class</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal insufficiency, acute renal failure may be due to an immune mechanism or to</td>
</tr>
<tr>
<td></td>
<td>circulatory failure.</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Toxic doses of quinine may induce abortion, but it is unwise to withhold the drug</td>
</tr>
<tr>
<td></td>
<td>if less toxic anti-malarials are not available</td>
</tr>
</tbody>
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**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 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, coma, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. High doses of quinine are teratogenic and may cause miscarriage. Fatalities have been reported in adults after doses of 2-8g. 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. Each 300 mg tablet is equivalent to 248 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 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-methanol-quinolone antimalarial agent which is 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*. The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite. 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 reduction in both its apparent volume of distribution and its clearance.

*Absorption:* Quinine is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation are 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 to 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 significantly by malaria infection, with reductions in both the 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 bile and saliva. Quinine crosses the placenta and is excreted in breast milk.

5.3. Preclinical Safety Data

Not applicable.

6.1 List of excipients
Lactose, Colloidal Silicon Dioxide, Potato Starch, Magnesium Stearate, Sodium Starch Glycollate (Type A), Sodium Lauryl Sulfate, Talc, Gelatin, Sucrose, Titanium Dioxide (E171), Carnauba Wax.

6.2 Incompatibilities
None known.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Tablet Containers: Do not store above 25°C. Store in the original container. Keep the container tightly closed.
Blisters: Do not store above 25°C. Store in the original package. Keep container in the outer carton.

6.5 **Nature and contents of container**
HDPP tablet containers with LDPE caps of 500 tablets.

Al/PVC blisters enclosed in an outer carton, pack sizes 28 and 56 tablets.

6.6 **Special precautions for disposal**
Not applicable.

7 **MARKETING AUTHORISATION HOLDER**
Bristol Laboratories Ltd
Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire HP4 1EG
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 17907/0011

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
21/03/2006
10 DATE OF REVISION OF THE TEXT

21/04/2016