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

For the treatment of falciparum (malignant tertian) malaria

Adults (*including elderly*) and Children aged 12 years and above: 600mg quinine sulphate every 8 hours for 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 aged 10-12 years: 10mg/kg bodyweight every 8 hours for 7 days. Children under 10 years: Not recommended.

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 assess the need for continuation of treatment with quinine.

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.
• Haemolysis or Haemoglobinuria
• Optic neuritis
• Tinnitus
• Myasthenia gravis, quinine may cause severe respiratory distress and dysphagia in these patients.
• As quinine has been implicated in precipitating blackwater fever, it is generally contraindicated in patients who have already suffered an attack.

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.

Serious hypersensitivity reactions including Stevens-Johnson syndrome have been reported with quinine.

Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency

• Quinine has been implicated in precipitating blackwater fever when given for prolonged periods, although in some cases, glucose-6-phosphate dehydrogenase deficiency may be at increased risk of haemolysis during quinine therapy and may develop acute haemolytic anaemia. 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 has dose-dependent QT-prolonging effects. Caution is recommended in patients with conditions which predispose to QT-prolongation and in patients with atrioventricular block. Quinine should be used with caution in patients with atrial fibrillation, heart block, other cardiac conduction defects, or other serious heart disease. Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants

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.
Caution is advised when administering quinine with drugs which could prolong the QT interval.
Quinine may increase the levels of phenobarbital and of carbamazepine.
Patients should be monitored closely during concomitant use of quinine with these agents.

Effect of Quinine on other drugs

The plasma concentration of flecainide, digoxin and mefloquine may be increased.
Ciclosporin: Quinine can decrease serum plasma concentrations of ciclosporin.
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).
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, pimozide, thioridazine and halofantrine.
Hypoglycaemics: There is an increased risk of hypoglycaemia when taken concurrently.
Anticoagulants: Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants.
Caution is advised when administering quinine with drugs which could prolong the QT interval.

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: 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.
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 astemizole and 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.
Quinine may increase the levels of phenobarbital and of carbamazepine. Patients should be monitored closely during concomitant use of quinine with these agents.

4.6 Fertility, pregnancy and lactation

Pregnancy

Large doses of quinine can induce abortion. 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 contraindication 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

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to <1/1000); Very rare (<1/10000); Not known (cannot be estimated from the available data).

MedDRA system organ class	**Adverse Reaction**
	Frequency
	Not known

Blood and lymphatic system disorders	Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, haemolytic-uremic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura
Immune system disorders	Eczematous dermatitis, oedema, erythema, lichen planus. Hypersensitivity reactions including asthma, angioneurotic oedema, photosensitivity, hot and flushed skin, pruritus, thrombocytopenic purpura, urticaria and fever
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Agitation, confusion
Nervous system disorders	Headache, vertigo, excitement, loss of consciousness, coma and death
Eye disorders	Blurred vision, defective colour perception, visual field constriction
Ear and labyrinth disorders	Tinnitus, impaired hearing
Cardiac disorders	Atrioventricular conduction disturbances, a fall in blood pressure coupled with a feeble pulse, prolongation of the QT interval, widening of the QRS complex and T wave flattening
Respiratory, thoracic and mediastinal disorders	Bronchospasm, dyspnoea.
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain*
Skin and subcutaneous tissue disorders	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritus, photosensitivity, Stevens-Johnson syndrome
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), oliguria.
Reproductive system and breast disorders	Abortion**
General disorders and administration site conditions	Cinchonism***

* May occur after long term administration of quinine.

** Toxic doses of quinine may induce abortion, but it is unwise to withhold the drug if less toxic antimalarials are not available.

*** 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 (blurred vision, defective colour perception, visual field constriction and total blindness).

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 or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

Acute intoxication can be seen after ingestion of doses of 4-12g, but a dose of 8g can prove lethal. The average fatal dose for an adult is about 8g although deaths have been reported from as little as 1.5g in an adult and 900mg in a child.

Symptoms

Quinine overdosage may lead to serious side effects including irreversible visual loss, and can be fatal. Symptoms include vomiting, tinnitus, deafness, headache, vasodilation 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 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 tablet is equivalent to 165mg quinine base, each 300mg tablet is equivalent to 248mg quinine base.

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

Pharmacotherapeutic group: Quinine alkaloid.

ATC Code: P01B C01.

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.

Pharmacodynamic effect

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.

Mechanism of Action

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 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 2-7% of those in the plasma.

Biotransformation: 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 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 AUTHORISATION HOLDER

Crescent Pharma Limited
Key House, Sarum Hill,
Basingstoke, RG21 8SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/1072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/03/2004

10 DATE OF REVISION OF THE TEXT

11/03/2026