SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Quinine Sulfate 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains quinine sulfate 200mg

Excipient(s) with known effect

Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

A white, biconvex film-coated tablet, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of chloroquine resistant falciparum malaria in adults and children aged 5 years or older (and ≥ 20kg)

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 chloroquine resistant falciparum malaria
Adults (including the elderly) and children aged 12 years and over: 600mg of quinine sulfate given 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.

Note
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.

If part or all of the dose is vomited within 1 hour of administration, then the same amount must be administered immediately.

For the treatment and prevention of nocturnal leg cramps

Adults (including the elderly):

The recommended dose is 200mg at bedtime. 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.

Paediatric population

Treatment of chloroquine resistant falciparum malaria
The dosage regimen for children by mouth is 10mg of quinine sulfate per kg body weight given every 8 hours for 7 days. Quinine sulfate 200mg tablets are not suitable for children weighing less than 20kg or less than 5 years old.

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
- Tinnitus
- Optic neuritis
- Haemoglobinuria
- Myasthenia gravis (quinine may cause severe respiratory distress and dysphagia in these patients)

4.4 Special warnings and precautions for use

Chinchonism
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.

Cardiac disorders
Quinine should be used with caution in patients with atrial fibrillation, conduction defects and heart block or other serious heart disease. It may cause hypoprothrombinaemia.

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.

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 should be monitored in all patients in case signs of resistance develop.

Use for nocturnal leg cramps
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).

Thrombocytopenia
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.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine, as it contains lactose.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on quinine

CYP3A4 substrate
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 such as 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 mefloquine may be increased.

Amantadine: Quinine can reduce the renal clearance of amantadine.

If quinine is administered the maintenance dose of digoxin should be halved.

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. Quinine has been reported to increase serum digoxin concentrations and quinine has reduced total body clearance of digoxin.

Other drug interactions

Drug caused QT prolongation
There is an increased risk of ventricular arrhythmias when quinine is given in combination with other drugs that prolong the QT interval, including amiodarone, moxifloxacin, pimozide, thioridazine, terfenadine and halofantrine and therefore concomitant use with these products should be avoided.

Caution is advised when administering quinine with drugs which could prolong the QT interval.

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.

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.

Anticoagulants: Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants. In one report, reductions in warfarin dosage were necessary after ingestion of large amount of tonic water containing quinine.

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

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.

There is an increased risk of inducing ventricular arrhythmias if quinine is given with halofantrine. There may be increased risk of convulsions when quinine is given with mefloquine.

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

Concomitant use of artemether and lumefantrine should be avoided.

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

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

Suxamethonium: Quinine enhances the neuromuscular effects of suxamethonium.

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

Anti-epileptics: 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
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 chloroquine-resistant strains of falciparium 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. However, quinine sulfate should not be given to nursing mothers unless the benefits outweigh the risks.

Fertility
The effects of quinine on fertility are unknown.

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. In 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 uraemic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura.
Immune system disorders	Reports have been received of eczematous dermatitis, oedema, erythema and lichen planus. Hypersensitivity reactions such as angioneurotic oedema, photosensitivity, hot and flushed skin, pruritus, thrombocytopenic purpura and urticaria have also been reported.
Metabolism and nutritional disorders	Hypoglycaemia may occur after oral administration although it is more common after parenteral administration.
Psychiatric disorders	Agitation and confusion.
Nervous system disorders	Reports of headache, vertigo, excitement, loss of consciousness, coma and death have been received.
Eye disorders	Blurred vision, defective colour perception, visual field constriction, total blindness.
Ear and labyrinth disorders	Tinnitus, hearing impaired.
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 has been noted with therapeutic doses.
Respiratory, thoracic and mediastinal disorders	Bronchospasm, dyspnoea, asthma may occur.
Gastrointestinal Disorders	Nausea, vomiting, diarrhoea, abdominal pain, fever may occur after long term administration of quinine.
Skin and subcutaneous tissue disorders	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritus, photosensitivity, Stevens-Johnson syndrome.
Musculoskeletal and	Muscle weakness may occur, aggravation of

connective tissue disorders	myasthenia gravis.
Renal and urinary disorders	Renal insufficiency and acute renal failure may be due to an immune mechanism or 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.
General disorders and administration site conditions	Fever

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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. 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.

Note:
Each quinine sulfate 200mg tablet is equivalent to 165mg of 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

Pharmacotherapeutic group: Antimalarials; Methanolquinolines, ATC Code: P01BC01.

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 exoerythrocyctic 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.

Quinine increases the refractory period of muscle so that the tetanic stimulation is diminished. It also affects a number of other body systems including the central nervous system, the cardiovascular system, the gastrointestinal tract and the pancreas. In addition, quinine exhibits local anaesthetic action and a local irritant action. As an antimalarial drug it acts primarily as a schizontocide. It is more toxic and less effective than chloroquine, but is especially useful for treatment of chloroquine-resistant strains of malarial infection.

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 1-3 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 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

No data of relevance to the prescriber, which is additional to that included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline cellulose
Maize starch
Colloidal anhydrous silica
Purified talc
Magnesium stearate
Sodium starch glycollate

Coating Components/Tablet
Methylhydroxypropylcellulose
Opadry white Y-1-7000 (containing methylhydroxypropylcellulose, titanium dioxide, polyethylene glycol 400)
Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC (285µm)/aluminium (25µm) foil blisters

Pack sizes: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250 and 500

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS

Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0200

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/10/2016

10 DATE OF REVISION OF THE TEXT

11/04/2018