SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Quinine Bisulphate Tablets BP 300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains quinine bisulphate 300mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

A white, biconvex film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of falciparum malaria
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

For falciparum malaria
Adults: the adult dosage regimen by mouth is 600mg of quinine sulphate given every 8 hours for 7 days.

The elderly: as for adults

Children: the dosage regimen for children by mouth is 10mg of quinine sulphate per kg body weight given every 8 hours for 7 days.

Note
If quinine resistance is known or suspected in the patient, then supplementary treatment with another recommended antimalarial drug is necessary.

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 elderly):

The recommended dose is 300mg at bedtime.
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.

4.3 Contraindications

-Hypersensitivity to quinine or any of the other ingredients
-Tinnitus
-Optic neuritis
-Acute haemoglobinuria
- Myasthenia gravis

4.4 Special warnings and precautions for use

Cinchonism
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).

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.

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.

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

Quinine should not be withheld from pregnant women who have life threatening malaria (see section 4.6).

Quinine can affect the results of certain urine tests for alkaloids and steroids. It may also interfere with tests for plasma catecholamines as well as slowing the erythrocyte sedimentation rate.

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

Excessive amounts of beverages containing quinine should not be consumed while taking quinine, as this may increase the risk of adverse reactions and toxicity.

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

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

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.

Amantidine: 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.

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 and halofantrine, and therefore concomitant use with these products should be avoided

Antiarrhythmmics: 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 thereby enhance the effect of anticoagulants.

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

Antimalarias: 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.

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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, which inhibits metabolism, may cause increased plasma quinine concentrations.

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 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 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

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 asthma, angioneurotic oedema, photosensitivity, hot and flushed skin, fever, pruritis, 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,*
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 have been noted with therapeutic doses.*
Respiratory, thoracic and mediastinal disorders	*Bronchospasm, dyspnoea may occur*
Gastrointestinal Disorders	*Nausea, vomiting, diarrhoea, abdominal pain may occur after long term administration of quinine,*
Skin and subcutaneous tissue disorders	*Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritus,*

	photosensitivity
Musculoskeletal and connective tissue disorders	*Muscle weakness, aggravation of myasthenia gravis*
Renal and urinary disorders	*Renal insufficiency, and 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.

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 visual disturbance.

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 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 bisulphate 300mg tablet is equivalent to 178mg 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

ATC Code: P01B C01. Quinine alkaloid (antimalarials, methanolquinolines).

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. malariar and P. vivax but not against mature gametocytes 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. Peak concentrations in the circulation are attained about 1-3 hours after ingestion.

Distribution: Plasma protein binding is about 70% in healthy subjects rising 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
Povidone K30
Ethanol
Sodium starch glycollate
Talc
Colloidal anhydrous silica
Magnesium stearate
Pregelatinised maize starch

Coating Components/Tablet

Purified Water
Isopropyl Alcohol
Hydroxypropylmethylcellulose
Diethyl phthalate
Opadry Y-1-7000 (containing hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol 400)
Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

AL/PVC Blister packs: 48 months

Polypropylene tablet containers: 36 months

6.4 Special precautions for storage

Store in a dry place below 25°C

6.5 Nature and contents of container

Polypropylene tablet containers with polyethylene caps and optional use of polyethylene ullage fillers

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 Shasun (UK) Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma Limited

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0058

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 February 1998 / 11 October 2004

10. DATE OF REVISION OF THE TEXT

24.05.2016