SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Quinine Sulphate 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg quinine sulphate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, scored, film-coated tablets, with Remedica's logo on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1). Treatment of Plasmodium falciparum (malignant tertian) malaria.

2). Treatment and prevention of nocturnal leg cramps in adults and elderly, when cramps cause regular disruption of sleep.

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 in known or suspected on completion of the course additional treatment may be given. This may be one of the following:
- doxycycline 200 mg daily (as a single dose or in divided doses) for at least 7 days.
- clindamycin 300 mg four times daily for 5 days.

Children under 12 years of age:

Dosage is dependent 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 200 mg at bedtime. The maximum dose is 300 mg. 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 Method of administration

Oral administration.

4.4 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.

4.5 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.

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 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 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.

- 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, 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.

- 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.

4.6 Special warnings and precautions for use-Paediatric population

Refer to section 4.5 “Special warnings and precautions for use”

4.7 Interaction with other medicinal products and other forms of interaction

Effects 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.

Amantadine: Quinine can reduce the renal clearance of amantadine.

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 drugs interactions

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

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.

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 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.

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.

4.8 Interaction with other medicinal products and other forms of interaction – Additional information on special populations

Refer to section 4.7 “Interaction with other medicinal products and other forms of interaction”

4.9 Interaction with other medicinal products and other forms of interaction – Paediatric population

Refer to section 4.7 “Interaction with other medicinal products and other forms of interaction”

4.10 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 sulphate 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 sulphate should not be used during pregnancy to treat cramps.

Breast-feeding
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.

4.11 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.

4.12 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. 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 disorder	Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolyticuremic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura
Immune system disorders	Eczematous dermatitis, oedema, erythema and lichen planus, hypersensitivity reactions including angioneurotic oedema, asthma, photosensitivity, hot and flushed skin, pruritis, thrombocytopenic purpura, urticarial and fever have also been reported
Metabolism and nutrition disorders	Hypoglycaemia may occur after oral administration

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, 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
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, 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 anti-malarials are not available

4.13 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 2-8 g. 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

Pharmacotherapeutic group*:* Antiprotozoals; Antimalarials*,* ATC Code*:* P01BC01

Quinine is a cinchona alkaloid and a 4-methanol-quinolone 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*. 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 sulphate.

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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone
Microcrystalline cellulose
Pregelatinised starch
Sodium lauryl sulfate
Colloidal silicon dioxide
Magnesium stearate
Talc

Coating
Hypromellose
Macrogol 400
Titanium dioxide
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25 °C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack size of 100 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Date of first authorization:

10. DATE OF REVISION OF THE TEXT

For internal use only: rw-spc-quinine-sulphate-fc-tabs-v01-r00-a0