SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Quinine Sulfate 200mg Tablets B.P.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 200mg Quinine Sulfate.

Also contains lactose and sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sugar coated tablets

White, round, biconvex sugar coated tablets

Tablet size (10.0 mm – 10.5 mm)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Treatment of uncomplicated attacks of falciparum malaria due to chloroquine or multi-drug resistant strains.

b) 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 treatment of uncomplicated (falciparum) malaria:

Adult (including elderly) and children aged 12 years and over: 600mg of Quinine Sulfate every eight 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.

Quinine should usually be combined (simultaneously or sequentially) with a second anti-malarial agent such as doxycycline (adults) or clindamycin (pregnant women and children). For further guidance please refer to the 'UK malaria treatment guidelines 2016'.

Children aged 11 years and under: Equivalent of 10mg/kg Quinine Sulfate every eight hours for 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

- Known hypersensitivity to quinine or any of the excipients in the tablet
- Haemoglobinuria
- Optic neuritis
- Tinnitus
- Myasthenia gravis, quinine may cause severe respiratory distress and dysphagia in these patients.

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 section 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

- Quinine should be used with caution in patients with atrial fibrillation 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 increased risk of haemolysis during quinine therapy. Quinine may aggravate the symptoms of myasthenia gravis.

- 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.

- 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 nonpharmacological 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.

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

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

Lactose and sucrose warning

- Patients with rare hereditary problems of galactose intolerance, fructose intolerance or sucrose-isomaltase insufficiency, total lactase deficiency or glucose-galactose malabsorption 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.

Effect of quinine on other drugs

The plasma concentration of mefloquine may be increased. Concomitant administration of mefloquine and quinine may produce electrocardiogram abnormalities and increase the risk of convulsions.

Amantadine: Quinine can reduce the renal clearance of amantadine.

Ciclosporin: Quinine can decrease 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

There is an increased risk of ventricular arrhythmias with other drugs which prolong the QT interval, including amiodarone, moxifloxacin, pimozide, thioridazine and halofantrine. Co-administration of other drugs known to alter cardiac conduction (e.g. antiarrhythmic or ß-adrenergic blocking agents, calcium channel blockers, some antihistamines or H1-blocking agents, tricyclic antidepressants and antipsychotics) might also contribute to a prolongation of 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 reduced the serum levels of quinine, therefore reducing its therapeutic effect.

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

Anticoagulants Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants, i.e. Warfarin.

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. Chloroquine and quinine appear to be antagonistic when given together for *P falciparum* malaria. There is a decrease in plasma concentrations of primaquine.
Concomitant use of quinidine may increase the possibility of cinchonism.

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: Clearance of quinine was reduced and half-life increased in patients pre-treated with cimetidine.

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 falciparum malaria: Pregnancy in patients 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.

Lactation

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.

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 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	Generalised hypersensitivity reactions including angioneuro oedema, fever, asthma, photosensitivity, hot and flushed sk pruritis, thrombocytopenic purpura and urticaria. Reports h been received of eczematous dermatitis, oedema, erythema lichen planus.
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, hypotension, prolongation of the QT interval, widening of the QRS comp and T wave flattening
Respiratory, thoracic and mediastinal disorders	Bronchospasm, dyspnoea
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain after long term administration of quinine
Skin and subcutaneous tissue disorders	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritis, photosensitivity
Musculoskeletal and connective tissue disorders	Muscle weakness, aggravation of myasthenia gravis
Renal and urinary disorders	Renal insufficiency, acute renal 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 n available

Reporting of side effects
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

Symptoms:

Quinine over dosage may lead to serious and irreversible side effects and can be fatal. In acute over dosage, symptoms of cinchonism may occur, including convulsions, nausea, vomiting, tinnitus, deafness, headache, vasodilatation, disturbed vision, QT prolongation and renal failure**.** The visual disorders may be severe and there may be

impairment of consciousness, coma, respiratory depression, arrhythmia and cardiogenic shock. Fatalities have been reported in adults after doses of 2 – 8 g. 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 30 mg/kg of quinine base has been taken.

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 activity.

Other treatment is mostly symptomatic to maintain blood pressure, respiration, renal function and treating arrhythmia, convulsions, hypoglycaemia and acidosis.

Note: that each 200 mg tablet is equivalent to 165 mg quinine base, each 300 mg tablet is equivalent to 248 mg quinine base.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: P01BC01. Quinine alkaloid

Quinine is a rapidly acting blood schizontide 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 P. falciparum gametocytes. Since it has no activity against exoerythrocytic forms quinine does not produce a radical cure in vivax or ovale malarias. Quinine supresses the asexual cycle of development of the malarial parasite in the erythrocytes through interference with its DNA.
On skeletal muscle quinine has dual action; it acts directly on muscle fibre and also effects muscular transmission by increasing the threshold of excitability of the motor end-plate.

5.2 Pharmacokinetic properties

Quinine is rapidly and almost completely absorbed from the gastro-intestinal tract. Peak concentrations in the circulation are attained about 1 to 3 hours after ingestion. About 70% is bound to proteins in plasma in healthy subjects rising to 90% in patients with malaria. Quinine is widely distributed throughout the body. Concentrations in CFS are 2 to 7% of those in the plasma. Quinine is extensively metabolized in the liver and excreted in the urine. Unchanged quinine in urine vary from less than 5 to 20%. Excretion is increased in acid urine. Elimination half-life is about 11 hours in healthy subjects but may be prolonged in patients with malaria. Pharmacokinetics are altered significantly by malarial infection, with reduction in volume of distribution and clearance.

5.3 Preclinical safety data

NA

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Lactose
Magnesium Stearate
Stearic Acid
Talc
Sodium Croscarmellose
Opaglos
Sucrose
Titanium Dioxide

6.2 Incompatibilities

None known

6.3 Shelf life

5 years

6.4 Special precautions for storage

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

Blisters: Do not store above 25°C. Keep the blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

Plastic securitainer with tamper evident polypropylene lids.
Available in pack sizes of 25, 50, 100, 250, 500 & 1000 tablets.

Blister packs of 0.25mm PVC and 20 microns Aluminium foil.
Available in pack sizes of 28 & 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmvit Limited
177 Bilton Road,
Perivale, Greenford,
Middx, UB6 7HQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 4556/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/07/2024

10 DATE OF REVISION OF THE TEXT

16/07/2024