ALPAQUINE

(Quinine Sulphate Tablets BP 300 mg)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

ALPAQUINE

(Quinine Sulphate Tablets BP 300 mg)

2. Qualitative and Quantitative Composition

Each Sugar Coated tablet contains:

Quinine Sulphate BP 300 mg

Colour: Titanium Dioxide BP

3. Pharmaceutical Form

Tablet

4. Clinical Particulars

4.1 Therapeutic indications

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

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 over: 600mg 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.

If quinine resistance is known or suspected on completion of the course additional treatment may be given. This may be one of the followings:

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 11 years and under: 10mg/kg 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 assess the need for continuation of treatment with quinine.

Method of Administration

For oral administration

4.3 Contraindications

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

4.4 Special warning and special precaution 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.

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 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).

• 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, 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.

• 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.

4.5 Interaction with other medicinal products and form 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 flecanide, 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 drug interactions

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

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.

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.

Hypoglycaemics: There is an increased risk of hypoglycaemia when taken concurrently.

Suxamethonium: Quinine enhances the neuromuscular effects of suxamethonium.

Ulcer-healing drugs: Cimetidine inhibits quinine metabolism leading to 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 sulfate should not be used during pregnancy unless the benefits outweigh the risks.

Treatment 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.

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

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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reaction
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 (asthma, angioneurotic oedema,

	photosensitivity, hot and flushed skin, fever, pruritis, thrombocytopenic purpura and urticarial).
Metabolism and nutrition disorders	Hypoglycaemia.
Psychiatric disorders	Agitation, confusion.
Nervous system disorders	Headache, vertigo, excitement, loss of consciousness, coma, 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, T wave flattening.
Respiratory, thoracic and mediastinal disorders	Bronchospasm, dyspnoea.
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain*.
Skin and subcutaneous tissue disorders	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritis, 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.

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.

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 tetrogenic and may cause miscarriage. Hypokalaemia and hypoglycaemia may also occur.

Treatment

Childen (<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 300mg Quinine sulfate tablet is equivalent to 248mg 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. Multiple dose activated charcoal will enhance elimination.

Observe patients for at least 12 hours after ingestion. Monitor cardiac conduction and rhthym, 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherpeutic 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.

Pharmacodynamnic 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

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 GI 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.

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.

6.0 PHARMACEUTICAL EXCIPIENTS

6.1 List of excipients

1.	Dicalcium Phosphate BP
2.	Lactose BP
3.	Starch BP
4.	Sodium Starch Glycolate BP
5.	Sodium Lauryl Sulfate BP
6.	Magnesium Stearate BP
7.	Purified Talc BP
8.	Colloidal Silicon Dioxide BP
9.	Kyron BP
10.	Purified Water BP
11.	Croscarmellose Sodium BP
COATING MATERIALS	
12.	Bleached Shellac BP
13.	Isopropyl Alcohol BP
14.	Sugar BP
15.	Gelatin BP

16	Gum Acacia BP
17.	Sodium Methyl Paraben BP
18.	Sodium Propyl Paraben BP
19.	Titanium Dioxide BP
20.	Carbon Tetrachloride BP
21.	Carnaubawax BP
22.	Beeswax BP

6.2 Incompatibilities

None Known

6.3 Shelf life

36 months

6.4 Special precaution for storage

Store at temperature not exceeding 30°C. Protect from light.

6.5 Nature contents of container

Blister pack of 10 X 10 tablets in a carton.

500 Tablets in a jar.

6.6 Instruction for use handling and disposal

Keep out of reach of children.

7. Manufacturer name

ALPA LABORATORIES LIMITED
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8. Marketing Authority

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