

## 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

For excipients, see 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  $\geq 20\text{kg}$ )

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 chloroquine resistant falciparum malaria**

**Adults and adolescents (> 12 years of age):** the adult dosage regimen by mouth is 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.

**The elderly:** as for adults

**Children:** 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.

**Note**

If quinine resistance is known or suspected on completion of the course, then supplementary treatment with another recommended antimalarial drug is necessary. Official guidance should be adhered to.

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 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.

**Method of administration:**

Oral

**4.3 Contraindications**

- Hypersensitivity to quinine or any of the other ingredients in the tablet
- Tinnitus
- Optic neuritis
- Acute haemoglobinuria
- Myasthenia gravis (quinine may cause severe respiratory distress 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.

*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 sulphate 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.

#### *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*

Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency may develop acute haemolytic anaemia. 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 haemolysis 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.

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

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.

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.

## **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 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 flecainide, digoxin and mefloquine may be increased.

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.

There is an increased risk of convulsions when quinine is given with mefloquine.

Quinine can decrease serum plasma concentrations of ciclosporin

### **Other drug interactions**

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. 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.

Co-administration of other drugs known to alter cardiac conduction (e.g. anti-arrhythmic or  $\beta$ -adrenergic blocking agents, calcium channel blockers, some antihistamines or  $H_1$ -blocking agents, tricyclic antidepressants and antipsychotics) might also contribute to a prolongation of the QT interval.

There is an increased risk of ventricular arrhythmias when moxifloxacin is given with quinine. There is increased risk of ventricular arrhythmias when quinine is given with artemether/lumefantrine. Concomitant use of artemether and lumefantrine should be avoided.

Rifampicin can reduce the serum levels of quinine, therefore reducing its therapeutic effect.

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

Quinine may cause hypoprothrombinaemia and thereby enhance the effect of anticoagulants.

Quinine enhances the neuromuscular effects of suxamethonium.

Concurrent use of quinidine may increase the possibility of cinchonism.

Chloroquine and quinine appear to be antagonistic when given together for *P falciparum* malaria. There is a decrease in plasma concentrations of primaquine.

Quinine can reduce the renal clearance of amantadine. Concomitant use of amantadine should be avoided.

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

#### **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 sulphate should not be used during pregnancy unless the benefits outweigh the risks.

Treatment of chloroquine-resistant strains of *falciparum* 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 sulfate 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.

##### **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)

<i>MedDRA system organ class</i>	<i>Adverse Reaction</i>
<i>Blood and lymphatic system disorders</i>	Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolytic uraemic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura
<i>Immune system disorders</i>	Generalised hypersensitivity reactions including angioedema and fever
<i>Metabolism and nutritional disorders</i>	Hypoglycaemia
<i>Psychiatric disorders</i>	Agitation and confusion, excitement
<i>Nervous system disorders</i>	Headache, Vertigo, loss of consciousness, coma and death
<i>Eye disorders</i>	Blurred vision, defective colour perception, visual field constriction, total blindness
<i>Ear and labyrinth disorders</i>	Tinnitus, hearing impaired
<i>Cardiac disorders</i>	Atrioventricular conduction disturbances, hypotension, prolongation of the QT interval, widening of the QRS complex and T wave flattening
<i>Respiratory, thoracic and mediastinal disorders</i>	Bronchospasm, dyspnoea, asthma
<i>Gastrointestinal Disorders</i>	Nausea, vomiting, diarrhoea, abdominal pain,

<i>Skin and subcutaneous tissue disorders</i>	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritus, photosensitivity
<i>Musculoskeletal and connective tissue disorders</i>	Muscle weakness, aggravation of myasthenia gravis
<i>Renal and urinary disorders</i>	Renal insufficiency, acute renal failure
<i>Reproductive system and breast disorders</i>	Toxic doses of quinine may induce abortion

### **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](http://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.

Symptoms include nausea, vomiting, tinnitus, deafness, headache and visual disturbance.

Features of a significant overdose include convulsions, impairment of consciousness, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. High doses of quinine are teratogenic and may cause miscarriage. Hypokalaemia and hypoglycaemia may also occur. Fatalities have been reported in adults after doses of 2-8g.

### **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.

Consider activated charcoal (50g for adults; 4g/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: P01BC01

Quinine 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 *P. falciparum* gametocytes. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias. It is more toxic and less effective than chloroquine, but it is especially useful for treatment of chloroquine-resistant strains of malarial infection.

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. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias.

### **5.2 Pharmacokinetic properties**

Quinine is rapidly and almost completely absorbed from the gastrointestinal tract. Peak concentrations in the circulation are attained about 1-3 hours after ingestion and about 70% is bound to proteins in the plasma in healthy subjects rising to about 90% in patients with malaria. Quinine is widely distributed throughout the body. Concentrations attained in the CSF are about 2-7% of those in the plasma. Quinine is extensively metabolised in the liver and excreted in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5% to 20%. 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. The pharmacokinetics of quinine are altered significantly by malaria infection, with reductions in both the apparent volume of distribution and clearance.

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**

28/04/2017