Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Quinine Sulphate 300 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg Quinine Sulphate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, circular, biconvex film-coated tablets with the identifying letters QD embossed on one face..

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1) In the treatment of malignant tertian malaria including treatment of chloroquine resistant malaria.
2) Treatment and prevention of nocturnal leg cramps in adults and the elderly, when cramps cause regular disruption of sleep (see section 4.2 and 4.4 and 4.8).

4.2 Posology and method of administration

Posology

For the treatment of falciparum malaria:

Adults (including elderly) and children over 12 years:
600 mg 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 following:

1. doxycycline 200 mg daily (as a single dose or in two divided doses) for at least 7 days.
2. clindamycin 300 mg four times daily for 5 days.

Children under 12 years:
10 mg/kg every eight hours for 7 days.

For the treatment and prevention of nocturnal leg cramps:

Adults (including elderly):

300 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.

Children and adolescents:
Quinine sulphate is not indicated to treat nocturnal leg cramps in children and adolescents.

Method of Administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Haemoglobinuria
- Optic neuritis
- Tinnitus
- Myasthenia gravis, quinine may cause severe respiratory distress and dysphagia in these patients.
- History of thrombocytopenia (see section 4.4)
- History of cardiac arrhythmias

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 'Undesirable effects' and 'Overdose').

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
Glucose-6-phosphate dehydrogenase deficient patients with malaria or taking quinine 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 (see section 'Fertility, pregnancy and lactation').

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 above and sections 'Interaction with other medicinal products and other forms of interaction' and 'Undesirable effects'), 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. Elderly people who develop thrombocytopenia are at risk of intra-cerebral haemorrhage.
Quinine sulphate should not be used for this indication during pregnancy (see section 'Fertility, pregnancy and lactation').

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on quinine

CYP 3A4 substrate

Quinine is metabolised via hepatic oxidative cytochrome P450 pathways, predominantly by CYP 3A4. 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 CYP 3A4 substrates, especially those causing prolongation of the QT interval.

Effect of quinine on other drugs
Quinine can decrease plasma concentrations of ciclosporin.

Quinine may increase the levels of phenobarbital and of carbamazepine. Patients should be monitored closely during concomitant use of quinine with these agents.

Other drug interactions

Drug caused QT prolongation
Caution is advised when administering quinine with drugs which could prolong the QT interval.

Amantadine: Quinine can reduce the renal clearance of amantadine.

Anti-arrhythmics: 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.

Other 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. There is an increased risk of ventricular arrhythmias with drugs which prolong the QT interval including halofantrine.

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.

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.

Quinidine: Concomitant use of quinidine may increase the possibility of cinchonism.

Chloroquine: Chloroquine and quinine appear to be antagonistic when given together for *P.falciparum*.

Suxamethonium: Quinine enhances the neuromuscular effects of suxamethonium.

Ulcer-healing drugs: Cimetidine inhibits quinine metabolism leading to 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 Falciparium 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.

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 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.

Blood and the lymphatic system disorders: thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolyticuremic syndrome, pancytopenia, haemolysis, agranulocytosis and thrombocytopenic purpura have all been reported.

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, petechiae, thrombocytopenic purpura and urticaria have also been reported.

Metabolism and nutrition disorders: hypoglycaemia may occur after oral administration although it is more common after parenteral administration.

Psychiatric disorders: agitation, confusion.

Nervous system disorders: reports of headache, vertigo, excitement, loss of consciousness, coma, cerebral haemorrhage and death have been received.

Eye disorders: blurred vision, defective colour perception, visual field constriction, total blindness.

Ear and labyrinth disorders: tinnitus, impaired hearing

Cardiac disorders: There may be 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 has been noted with therapeutic doses.

Respiratory, thoracic and mediastinal disorders: bronchospasm and dyspnoea may occur.

Gastrointestinal disorders: diarrhoea, nausea, vomiting and abdominal pain may occur after long term administration of quinine.

Liver and biliary tract: hepatotoxicity.

Musculoskeletal, connective tissue and bone disorders: muscle weakness, aggravation of myasthenia gravis.

Skin and subcutaneous tissue disorders: Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritus, photosensitivity, Stevens-Johnson syndrome.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
Quinine overdosage may lead to serious and irreversible side effects and can be fatal. In acute overdosage, symptoms of cinchonism may occur, including convulsions, nausea, vomiting, tinnitus, deafness, headache, vasodilation and disturbed vision. The visual disorders may be severe and there may be impairment of consciousness, coma, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. Hypokaleamia and hypoglycaemia may also occur. Fatalities have been reported in adults after doses of 2-8g. High doses of quinine are tetrogenic and may cause miscarriage.

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 of quinine sulphate 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: Anti-protozoals, quinine alkaloids, other drugs for disorders of the musculoskeletal system
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.

Pharmacodynamic 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

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.

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 sulphate. 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.

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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet contains:

Sodium Laurilsulfate
Povidone
Microcrystalline Cellulose
Croscarmellose Sodium
Magnesium Stearate
Hydrogenated Vegetable Oil.

The coating contains:
Hypromellose
Hydroxypropyl Cellulose
Medium Chain Triglycerides
Macrogol 3350
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene tablet containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids. Also amber glass bottles with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:
a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC.
(ii) Surface printed 20µm hard temper aluminium foil

Pack sizes: 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250, 500, 1,000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/052/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 July 1985

Date of last renewal: 04 July 2010

10 DATE OF REVISION OF THE TEXT

May 2023