SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Sterile Quinine Dihydrochloride Concentrate BP 600mg/2ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2 ml contains:
Quinine dihydrochloride BP 600 mg
Water for Injection BP Q.S.

3. PHARMACEUTICAL FORM
Solution for Injection
A clear colourless to very pale yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
For the treatment of acute attacks of malaria, including attacks due to chloroquine-resistant or multi-drug-resistant strains of Plasmodium falciparum. Quinine is used parenterally for cerebral, severe or complicated malaria, or when vomiting prevents retention of an orally administered drug.

4.2 Posology and method of administration
Intravenous Administration
An initial dose of 16.4 mg (equivalent to 20 mg of dihydrochloride)/kg is infused over 4 hours followed by 8.2 mg (equivalent to 10 mg of dihydrochloride)/kg every 8 hours in adults and every 12 hours in children. The initial dose should be halved if the patient has received quinine, quinidine or mefloquine during the previous 12-24 hours. The maintenance dose should be reduced threefold in patients with impaired renal function.
Where facilities for I.V. infusion do not exist, quinine I.M. can be administered in the same dosage. The required dose should be divided equally between two sites, one in each anterior thigh. Whenever parenteral quinine is used, oral treatment should be resumed as soon as the patient is able to take it, and continued for the completion of the course.

4.3 Contraindications
Quinine is contraindicated in patients with the following:
Prolonged QT interval
One case of a fatal ventricular arrhythmia was reported in an elderly patient with a prolonged QT interval at baseline, who received quinine sulfate intravenously for P. falciparum malaria **.**
Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency
Hemolysis can occur in patients with G6PD deficiency receiving quinine**.**
Known Hypersensitivity Reactions to Quinine or any of the Excipients.
These include, but are not limited to; the following :
Thrombocytopenia
Idiopathic thrombocytopenia purpura (ITP) and Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Blackwater fever (acute intravascular hemolysis, hemoglobinuria, and hemoglobinemia)
Known Hypersensitivity to Mefloquine or Quinidine
Cross-sensitivity to quinine has been documented .
Myasthenia Gravis
Quinine has neuromuscular blocking activity, and may exacerbate muscle weakness.
Optic Neuritis
Quinine may exacerbate active optic neuritis .

4.4 Special warnings and precautions for use

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 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.

Quinine should be used with caution in patients with atrial fibrillation, heart block, other cardiac conduction defects, or other serious heart disease. Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants.

Quinine has been implicated in precipitating black water fever when given for prolonged periods, although in some cases, glucose-6-phosphate dehydrogenase deficiency may have been involved. Patients with glucose-6-phosphate dehydrogenase deficiency may be at increased risk of haemolysis during quinine therapy and may develop acute haemolytic anaemia.

Owing to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 (pls refer to undesirable effects).

Hypersensitivity to quinine may also occur with symptoms of cinchonism together with urticaria, flushing, pruritis, rash, fever, angioedema and asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Amantadine

Reduced renal clearance of amantadine with risk of amantadine toxicity (including headache, nausea, and dizziness).

Analgesics

Increased risk of ventricular arrhythmias with levacetylmethadol (avoid concomitant use).

Anti-arrhythmics

Plasma concentration of flecainide increased. Increased risk of ventricular arrhythmias with other drugs which prolong the QT interval, including amiodarone (avoid concomitant use). Concomitant use of quinidine may increase the possibility of cinchonism.

Antibacterials

Increased elimination of quinine reported with rifampicin. There is an increased risk of ventricular arrhythmias with moxifloxacin.

Anticoagulants

Quinine may cause hypoprothrombinaemia and enhance effects of anticoagulants.

Anti-histamines

Increased risk of ventricular arrhythmias with astemizole and terfenadine.

Other antimalarials

There may be an increased risk of side effects if quinine is used with other antimalarials, for example, chloroquine, halofantrine and mefloquine (increased risk of convulsions), although this should not prevent their use in severe cases. Quinine may increase the plasma concentration of mefloquine.

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

There is an increased risk of ventricular arrhythmias with halofantrine.

Antipsychotics

Increased risk of ventricular arrhythmias with pimozide or thioridazine (avoid concomitant use).

Cardiac glycosides

Quinine may increase the plasma concentration of digoxin and it has been recommended that the maintenance dose of digoxin should be halved during concurrent therapy.

Ulcer healing drugs
Cimetidine inhibits metabolism (increased plasma quinine concentration).
Quinine can decrease plasma concentrations of ciclosporin.
Concurrent use with oral hypoglycemic may increase the risk of hypoglycemia.
Quinine enhances the neuromuscular effects of suxamethonium.
Renal Impairment
The effects of mild and moderate renal impairment on the safety and pharmacokinetics of quinine sulfate are not known. The clearance of quinine is decreased in patients with severe chronic renal failure. The dosage and dosing frequency should be reduced
Hepatic Impairment
Adjustment of the recommended dose is not required in mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, but patients should be monitored closely for adverse effects of quinine. Quinine should not be administered in patients with severe (Child-Pugh C) hepatic impairment.
Geriatric Use
Clinical studies of quinine sulfate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond to treatment differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
Large doses of quinine can induce abortion. Congenital malformations of the optic and auditory nerves have been reported after quinine has failed to induce abortion. Quinine sulphate should not be used during pregnancy unless the benefits outweigh the risks. However, pregnancy in a patient with malaria is not generally regarded as a contraindication to the use of quinine and it should not be withheld from pregnant women with life threatening malaria if other agents are inappropriate. 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. Infants at risk for glucose-6-phosphate dehydrogenase deficiency should not be breast-fed until this disease can be ruled out. However, quinine sulphate should not be given to nursing mothers unless the benefit outweighs 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

MedDRA system organ class	Adverse Reaction
Blood and lymphatic system disorders	Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, oliguria, haemolytic-uremic syndrome, pancytopenia, haemolysis, agranulocytosis, thrombocytopenic purpura
Immune system disorders	Generalised hypersensitivity reactions including angioneurotic oedema and fever
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Agitation, confusion
Nervous system disorders	Headache, vertigo

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 complex and T wave flattening
Respiratory, thoracic and mediastinal disorders	Bronchospasm
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain
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

4.9 Overdose

Acute intoxication can be seen after ingestion of doses of 4-12 g, but a dose of 8 g can prove lethal. The average fatal dose for an adult is about 8 g although deaths have been reported from as little as 1.5 g in an adult and 900 mg in a child.

Symptoms: Quinine overdosage may lead to serious side effects including irreversible visual loss, and can be fatal.

Symptoms include 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.

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.

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: Antiprotozoal, Antimalarial
ATC code: P01BC01
Quinine is a highly active blood schizonticide and suppresses the asexual cycle of development of malaria parasites in the erythrocytes. It has no action on the tissue forms of the malaria parasites and therefore will not prevent relapse of Plasmodium vivax, P. ovale or P. malariae infections

5.2 Pharmacokinetic properties

Quinine is almost completely absorbed from the gastrointestinal tract. Maximal blood concentrations are attained within one to three hours of ingestion. Most of the quinine is bound to plasma proteins. Quinine readily diffuses across the placenta. Quinine is extensively metabolized, mainly in the liver, and only a small proportion is excreted unchanged.

5.3 Preclinical safety data
Not known

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzyl alcohol, Sodium Hydroxide, Water for Injection

6.2 Incompatibilities
Not known

6.3 Shelf life
36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container and special equipment for use, administration or implantation
Pack of 10 x 2ml USP Type-I flint glass ampoule.

6.6 Special precautions for disposal <and other handling>
None.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.
C- 1101 /1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway, Goregaon (East)
Mumbai- 400 063, India.

8. MARKETING AUTHORISATION NUMBER(S)

07661/08457/REN/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14/02/2019
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11. Reference

https://ciplamed-library.com/content/qinarsol-tabetsinjection