1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

QUININE DIHYDROCHLORIDE 600mg/2ml Solution for Injection. (PENINE INJECTION)

2. Qualitative and quantitative composition

600mg/2ml QUININE DIHYDROCHLORIDE.

For full list of excipients see section 6.1

3. Pharmaceutical form

Sterile solution for injection.

A clear, colourless or 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 cerebreal, severe or complicated malaria, or when vomiting prevents retention of an orally administered drug. Quinine dihydrochloride is the salt usually employed for the preparation of injections.

4.2 Posology and method of administration

In severe or complicated malaria, when the patient is unable to take oral medication, a slow intravenous infusion of quinine is used. In severely ill adults, a loading dose of 20mg quinine dihydrohloride per kg may be administered by slow, constant rate intravenous infusion diluted in either isotonic fluid or 5% glucose solution (5-10ml per kg bodyweight depending on the patient's overall fluid balance) over four hours provided that the patient has not received quinine, quinidine or mefloquin during the previous twelve to twenty-four hours, and reliable hospital facilities are available, including cardiac monitoring. The maintenance dose is 10mg of quinine dihydrochloride per kg in 250 to 500ml of diuent, preferably 5% glucose solution, by intravenous infusion over four hours, repeated at eight to twelve hourly intervals. For children, a dose of 25 to 30mg per kg body-mass daily in three divided doses has been recommended.

Oral therapy should be substituted as soon as possible and a total of at least seven days therapy should be completed.

If, after forty-eight hours of parenteral treatment, the patient is still unable to take oral treatment, or if there is evidence of significant hepatic impairment, the maintenance dose should be reduced by half. The recommended drug dosage adjustment for patients with impaired renal function (ie, a GFR less than 10), is a third of the normal dose. However, the loading dose of quinine should not be reduced in patients with renal and hepatic impairment.

If intravenous infusion is not possible, quinine dihydrochloride may be given by intramuscular injection of 10mg per kg, although this may cause pain and local tissue necrosis. Monitoring of blood levels and side-effects is recommended during quinine therapy.

Note: Quinine should never be given by rapid intravenous “push” or bolus injections as this may cause severe or even fatal cardiovascular toxicity.

4.3 Contraindications

Quinine is contra-indicated in patients with a history of hypersensitivity to Quinine especially if it takes form of cutaneous, angioedematous, visual or auditory symptoms. It is also contra-indicated in the presence of haemolysis, and in patients with tinnitus or optic neuritis.

4.4 Special warnings and precautions for use

Quinine must be used with caution in patients with atrial fibrillation or other serious heart disease.

Quinine may aggravate symptoms of myasthenia gravis and should be used with care if at all in such patients.

Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants. Quinine must be stopped immediately if evidence of haemolysis appear.

Antimalarial agents and especially quinine, when given for prolonged periods, have been implicated in precipitating black water fever.

However, in some cases deficiency of glucose-6-phosphate dehydrogenase may have been involved. Glucose-6-phosphate dehydrogenase-deficient patients with malaria may be at increased risk of haemolysis during quinine therapy.

Pregnancy

Quinine should not be withheld from pregnant women with life-threatening malaria if other less hazardous agents are unavailable or inappropriate. Pregnant women seem to be particularly prone to quinine-induced hyperinsulinaemia and hypoglycaemia. Excessive doses may induce abortion, and congenital malformation of the optic and auditory nerves have been reported after failure to induce abortion with quinine.

When administered intravenously to pregnant patients, the infusion rate should not exceed 10mg/kg every eight hours.

4.5 Interaction with other medicinal products and other forms of interaction

1 Antacids and aluminum-containing preparations can delay or reduce the absorption of quinine;

2 Anticoagulant can be enhanced after combined with quinine;

3 Muscle relaxants such as succinylcholine, myostatin and other combines with quinine may cause respiratory depression;

4 If quinidine is combined with quinine, the cinchona reaction can be increased;

5 Urine basifying agent, such as sodium bicarbonate, can increase the reabsorption of quinine by renal tubules, resulting in an increase in the concentration and toxicity of quinine blood;

6 Combined with vitamin K can increase the absorption of quinine;

7 Combined with bupixidine, cyprozine, meclizine, phenothiazines, thioxanthens, trimethofenzamide, aminoglycoside antibiotics can cause tinnitus, dizziness;

8 In combination with nifedipine (nitrophenidine), the concentration of free quinine increases.

4.6 Fertility, pregnancy and lactation

Quinine should not be withheld from pregnant women with life-threatening malaria if other less hazardous agents are unavailable or inappropriate. Pregnant women seem to be particularly prone to quinine-induced hyperinsulinaemia and hypoglycaemia. Excessive doses may induce abortion, and congenital malformation of the optic and auditory nerves have been reported after failure to induce abortion with quinine.

When administered intravenously to pregnant patients, the infusion rate should not exceed 10mg/kg every eight hours.

4.7 Effects on ability to drive and use machines

None have been reported or are known.

4.8 Undesirable effects

Cinchonism Repeated doses of quinine in normal therapeutic doses may give rise to a cluster of symptoms known as cinchonism. In mild form this consists of ringing in the ears, headache, nausea and disturbed vision; however when medication is continued or after large single doses, gastro-intestinal, cardiovascular and dermal manifestations may appear.

Hearing and vision are particularly disturbed. Functional impairment of the 8^{th} nerve results in tinnitus, decreased auditory acuity, and verugio. Visual signs consists of blurred vision, disturbed color perception, photophobia, diplopia, night blindness, constricted visual fields, scotomata, mydriasis and rarely blindness. Marked spastic constriction of the retinal vessels occurs; the retina is ischaemic, the discs are pale and retinal oedema may ensue. In severe cases, optic atrophy results.

Visual disturbances are normally reversible but may be permanent, and may rarely include sudden blindness.

Gastro-intestinal symptoms are also prominent in cinchonism. Nausea, vomiting, abdominal pain and diarrhea result from local irritation, and the nausea and emesis also have a central basis.

The skin is often hot and flushed, and sweating is prominent. Rashes frequently appear. Angioedema, especially of the face, is occasionally observed.

Hypersensitivity: some patients are hypersensitive to quinine and even small doses may give rise to cinchonism together with other hypersensitivity reactions including angioedema and asthma.

Renal damage: renal damage may occur and anuria and uremia may ensue. Renal impairment may be due to an immune mechanism or to circulatory failure. The triad of massive haemolysis, haemoglobinaemia, and haemoglobinurea is a rare complication of quinine therapy in pregnant women or in patients with malaria. Quinine is capable of causing hypoprothrombinaemia; the simultaneous administration of vitamin K counteracts the prolongation of the prothrombin time.

Rarely, quinine may cause thrombocytopenic purpura in susceptible individuals by a thrombocytolytic action. In a few instances, the drug appears to have caused agranulogytosis.

Cardiovascular symptoms: quinine may cause distrubances in cardiac conduction and a reduction of blood pressure with syncope and circulatory failure; severe hypotension can also follow rapid injection of quinine.

Thransient ventricular tachycardia may rarely be observed after massive acute overdosage.

4.9 Overdose

Poisoning by quinine is usually due to clinical overdose or to hypersensitivity. Symptoms of overdosage include gastro-intestinal, central nervous system, cardiovascular disturbances, and other toxic symptoms mentioned under side-effects to an enhanced degree. Visual disturbances are usually reversible but may be permanent, and may rarely include sudden blindness.

CNS Symptoms are noted in more severe grades of poisoning, particularly headache, fever, vomiting, apprehension, excitement, confusion, delirium, and syncope.

Respiration is first stimulated and then shallow and depressed. The skin becomes cold and cyanotic as poisoning progresses, the body temperature and blood pressure fall, weakness is extreme and the pulse is feeble, coma ensues and death occurs from respiratory arrest.

Severe poisoning can produce convulsions, coma, respiratory depression and death.

The average fatal dose in adults has been reported to be about 8g. death may results in a few hours or may be delayed for one to two days.

If large doses of quinine or its salts have been recently ingested, the stomach should be emptied by aspirationand lavage.

Measured aimed at enhancing the elimination of quinine such as forced acid diuresis, haemodialysis, and haemoperfusion are largely ineffective because quinine is extensively metabolized in the liver. Blood pressure should be supported. Signs of haemolytic anaemia may be indicative of a need to treat acute renal failure. Assisted respiration may be necessary to combat respiratory failure.

Cardiac rhythm should be monitored.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: medicines against Protozoa

Pharmacological action:

Quinine acts primarily as a schizontocide ie it suppresses the asexual cycle of development of malaria parasites in the erythrocytes. It has little effect on sporozoites or pre-erythrocytic forms of malarial parasites. It does not, therefore, prevent the relapse of Plasmodium vivax infections.

Quinine is also gametocidal for P. vivax and P. malaria but not for P. falciparum, and therefore does not prevent transmission of this infection by the mosquito.

5.2 Pharmacokinetic properties

Plasma concentrations of quinine between 8 and 15mg/litre are effective clinically and are generally not toxic; such values are usually achieved with the standard therapeutic dose. Approximately 70% of quinine is bound to proteins in the plasma in healthy subjects, rising to about 90% in patients with malaria. The concentration in cerebrospinal fluid is about 2-5% of that in the plasma. Quinine is extensively metabolized, especially 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%. The metabolites are excreted in the urine; renal excretion of quinine is twice as rapid when the urine is acidic as when it is alkaline. The elimination half-life in healthy subjects is about eleven hours, but may be prolonged in patients with malaria. The pharmacokinetics of quinine may be altered significantly by malaria infection, with reductions in bot clearance and the apparent volume of distribution. Quinine crosses the placenta and is excreted in breast milk.

5.3 Preclinical safety data

QUININE DIHYDROCHLORIDE injection has been widely used for many years in clinical practice. There is nodata which adds significant information relevant to the prescriber, to that covered elsewhere in this document.

6. Pharmaceutical particulars

6.1 List of excipients

Hydrochloride acid

Activated charcoal

Water for Injections

6.2 Incompatibilities

None have been reported or are known.

6.3 Shelf life

The shelf life of the QUININE DIHYDROCHLORIDE injection is 36 months.

6.4 Special precautions for storage

Store below 25℃. Protect from light and moisture.

6.5 Nature and contents of container

QUININE DIHYDROCHLORIDE injection is supplied in boxes containing glass ampoules.

6.6 Special precautions for disposal and other handling

MARKETING AUTHORIZATION HOLDER:
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1.3.3 Package Insert (also known as patient information PIL)