E.D.P QUININE INJECTION

(Quinine Dihydrochloride Injection BP 300 mg/ml)

1. Name of the medicinal product

E.D.P QUININE INJECTION

Quinine Dihydrochloride Injection BP 300 mg/ml

2. Qualitative and Quantitative Composition

Each ml contains:

Quinine Dihydrochloride BP 300 mg

3. Pharmaceutical Form

Liquid Injection

4. Pharmacological Class:

Quinoline (cinchona alkaloids).

5. Product Description:

A white or almost white powder.

6. Clinical Particulars

6.1 Therapeutic Indication

For the treatment of falciparum malaria.

Treatment and prevention of nocturnal leg cramps in adults and the elderly, when cramps cause regular disruption of sleep

6.2 Pharmacodynamics

Quinine is used parenterally to treat life-threatening infections caused by chloroquine-resistant Plasmodium falciparum malaria. Quinine acts as a blood schizonticide although it also has gametocytocidal activity against P. vivax and P. malariae. Because it is a weak base, it is concentrated in the food vacuoles of P. falciparum. It is thought to act by inhibiting heme polymerase, thereby allowing accumulation of its cytotoxic substrate, heme. As a schizonticidal drug, it is less effective and more toxic than chloroquine. However, it has a special place in the management of severe falciparum malaria in areas with known resistance to chloroquine.

6.3 Mechanism of Action:

The theorized mechanism of action for quinine and related anti-malarial drugs is that these drugs are toxic to the malaria parasite. Specifically, the drugs interfere with the

parasite's ability to break down and digest hemoglobin. Consequently, the parasite starves and/or builds up toxic levels of partially degraded hemoglobin in itself.

TARGET	ACTIONS	ORGANISM
AFe(II)-protoporphyrin IX	antagonist	Plasmodium falciparum
UPlatelet glycoprotein IX	other	Human
UIntermediate conductance calcium-activated potassium channel protein 4	inhibitor	Human

6.4 Pharmacokinetic:

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.

Absorption, Distribution and Excretion

76 - 88%

Route of Elimination

Quinine is eliminated primarily via hepatic biotransformation. Approximately 20% of quinine is excreted unchanged in urine.

Volume of Distribution

1. 1.43 ± 0.18 L/kg [Healthy Pediatric Controls]
2. 0.87 ± 0.12 L/kg [P. falciparum Malaria Pediatric Patients]
3. 2.5 to 7.1 L/kg [healthy subjects who received a single oral 600 mg dose]

Clearance

1. 0.17 L/h/kg [healthy]
2. 0.09 L/h/kg [patients with uncomplicated malaria]
3. 18.4 L/h [healthy adult subjects with administration of multiple-dose activated charcoal]
4. 11.8 L/h [healthy adult subjects without administration of multiple-dose activated charcoal]
5. Oral cl=0.06 L/h/kg [elderly subjects]

- **Toxicity**

Quinine is a documented causative agent of drug induced thrombocytopenia (DIT). Thrombocytopenia is a low number of platelets in the blood. Quinine induces production of antibodies against glycoprotein (GP) Ib-IX complex in the majority of

cases of DIT, or more rarely, the platelet-glycoprotein complex GPIIb-IIIa. Increased antibodies against these complexes increases platelet clearance, leading to the observed thrombocytopenia.

- **Side effects**

Cinchonism or quinism is a pathological condition in humans caused by an overdose of quinine or its natural source, cinchona bark. Cinchonism can occur from therapeutic doses of quinine, either from one or several large doses, or from small doses over a longer period of time, not from the amounts used in tonic drinks, but possibly from ingestion of tonic water as a beverage over a lengthy period of time. Quinidine can also cause cinchonism.

In the United States, the Food and Drug Administration limits tonic water quinine to 83 parts per million, which is one-half to one-quarter the concentration used in therapeutic tonic.

It is usual for quinine in therapeutic doses to cause cinchonism; in rare cases, it may even cause death (usually by pulmonary oedema). The development of mild cinchonism is not a reason for stopping or interrupting quinine therapy and the patient should be reassured. Blood glucose levels and electrolyte concentrations must be monitored when quinine is given by injection; the patient should also ideally be in cardiac monitoring when the first quinine injection is given (these precautions are often unavailable in developing countries where malaria is most a problem).

Cinchonism is much less common when quinine is given by mouth, but oral quinine is not well tolerated (quinine is exceedingly bitter and many patients will vomit up quinine tablets): other drugs such as Fansidar® (sulfadoxine (sulfonamide antibiotic) with pyrimethamine) or Malarone® (proguanil with atovaquone) are often used when oral therapy is required. Blood glucose, electrolyte and cardiac monitoring are not necessary when quinine is given by mouth.

- **Quinine and pregnancy**

In very large doses, quinine also acts as an abortifacient (a substance that induces abortion). In the United States, quinine is classed as a Category X teratogen by the Food and Drug Administration, meaning that it can cause birth defects (especially deafness) if taken by a woman during pregnancy. In the United Kingdom, the recommendation is that pregnancy is *not* a contra-indication to quinine therapy for falciparum malaria (which directly contradicts the US recommendation), although it should be used with caution; the reason for this is that the risks to the pregnancy are small and theoretical, as opposed to the very real risk of death from falciparum

malaria. Further research, conducted in Sweden's Consug University hospital, has found a weak but significant correlation between dosage increase in pregnancy and Klebs-Loeffler bacillus infections in neonates.

- **Quinine and interactions with other diseases**

  Quinine can cause hemolysis in G6PD deficiency, but again this risk is small and the physician should not hesitate to use quinine in patients with G6PD deficiency when there is no alternative. Quinine can also cause drug-induced immune thrombocytopenic purpura (ITP).

  Quinine can cause abnormal heart rhythms and should be avoided if possible in patients with atrial fibrillation, conduction defects or heart block.

  Quinine must not be used in patients with hemoglobinuria, myasthenia gravis or optic neuritis, because it worsens these conditions.

- **Quinine and hearing impairment**

  Some studies have related the use of quinine and hearing impairment, which can cause some high-frequency loss, but it has not been conclusively established whether such impairment is temporary or permanent (DCP 1994).

- **Contraindication:**

  Quinine is contraindicated in patients with a history of hypersensitivity to quinine or any of the excipients in the tablet, in tinnitus or optic neuritis, in myasthenia gravis and in the presence of haemolysis or haemoglobinuria. As quinine has been implicated in precipitating blackwater fever, it is generally contraindicated in patients who have already suffered an attack.

- **Undesirable effects**

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

7. Pharmaceutical Excipient

7.1 List of excipients

Sodium Chloride

Water for Injection

7.2 Incompatibilities

Quinine Dihydrochloride Injection should not be mixed with other drugs in the same infusion solution or the same syringe.

7.3 Shelf life

36 months

7.4 Special Precautions for Storage

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

7.5 Nature and contents of container

2ml amber coloured sealed ampoule with blue dot at construction.

7.6 Special precautions for disposal and other handling

None

8. Manufacturer Name

Alpa Laboratories Limited

33/2 A.B Road, Pigdamber, Indore (MP)

Pin Code- 453446

+91 731 4294567

+91 731 4294444