

QUININE DIHYDROCHLORIDE 6%
(QUININE DIHYDROCHLORIDE) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Quinine dihydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinine Dihydrochloride 6% contains 600 mg quinine dihydrochloride in 10 mL of water for injections.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Quinine Dihydrochloride 6% is a sterile concentrated solution for injection which has a faint straw coloured appearance. Dilute before administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Quinine Dihydrochloride 6% Sterile Concentrate 600 mg in 10 mL solution for injection is indicated for the acute treatment of malaria. It may also be used in the treatment of Babesiosis in conjunction with clindamycin.

4.2 DOSE AND METHOD OF ADMINISTRATION

The solution should be diluted before administration and contains no antimicrobial preservative. Quinine Dihydrochloride 6% should be used in one patient on one occasion only and unused solution should be discarded.

Wherever possible, patients should be transferred to oral therapy as soon as possible.

For intravenous injection

Adults - The following doses may be used as a guide, Quinine Dihydrochloride 6% must be diluted in 500 mL of glucose 5% preferably, or sodium chloride 0.9% (usually 600 mg in 500 mL) and infused slowly over 4 hours.

Loading dose: 20 mg/kg up to a **maximum** of 1400 mg given slowly by infusion over 4 hours. Commence the maintenance doses 8 to 12 hours after loading dose.

Maintenance dose: 10 mg per kg up to a **maximum** of 700 mg over 4 hours given slowly by infusion. Repeat every 8-12 hours if necessary.

A loading dose is not required if anti-malarials have been given during the previous 24 hours.

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If parenteral therapy is required for more than 48 hours, the maintenance dose of quinine should be **reduced** by one third to one half to 5 mg/kg to avoid accumulation and drug level monitoring is important. See Section 4.4 Special Warnings and Precautions for Use.

Alternatively, in **Intensive Care Units only**, an initial loading dose of 7 mg per kg may be given over 30 minutes followed immediately by the first of the maintenance infusions.

Paediatric - Intravenous - 10 mg per kg diluted and infused **slowly** at a rate not exceeding 0.5 mg per minute, preferably with ECG monitoring.

Intramuscular injection

See Section 4.4 Special Warnings and Precautions for Use.

Compatible solutions

Glucose 5%, sodium chloride 0.9%.

4.3 CONTRAINDICATIONS

Quinine Dihydrochloride 6% is contraindicated in the following situations:

- Hypersensitivity to quinine or quinidine
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- History of Blackwater Fever
- Patients with tinnitus or optic neuritis
- It should not be used in the presence of haemolysis or in the presence of concurrent anticoagulant therapy
- It should not be used in patients with diabetes

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Check for hypersensitivity to quinine or quinidine BEFORE administration. It is important that when given intravenously it should be given by SLOW infusion and the patient observed closely for signs of cardiotoxicity.

Pulse and blood pressure should be closely monitored and the rate of infusion attenuated if dysrhythmias occur, and blood glucose concentrations should be monitored. Therapy should be changed to oral administration as soon as possible.

If intravenous infusion is not possible, quinine dihydrochloride has been given intramuscularly. This can be an irritant, cause pain, focal necrosis and abscess formation, and fatal tetanus has developed in some patients, and there have been concerns regarding its safety and efficacy. **The intramuscular route should only be used as a last resort.**

Haemolysis

Quinine Dihydrochloride 6% should be stopped immediately and supportive measures instituted if signs of haemolysis appear. Haemolysis with a potential for haemolytic anaemia has been reported when given to patients with G6PD deficiency.

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Prothrombin formation

Quinine Dihydrochloride 6% is capable of causing hypoprothrombinaemia and may enhance the effect of anticoagulants.

Atrial fibrillation

Patients with this condition should be digitilised before receiving quinine as otherwise it may cause an increase in the ventricular rate.

Hypersensitivity

Reactions include cutaneous flushing, pruritus, rash, fever, facial oedema, GI distress, dyspnoea, tinnitus, and impairment of vision. The most frequently reported hypersensitivity reaction is extreme flushing of the skin with intense pruritus. If evidence of hypersensitivity occurs, quinine therapy should be discontinued.

Use in hepatic impairment

The half-life of quinine is prolonged in hepatitis and moderate chronic liver disease.

Use in the elderly

No data available.

Paediatric use

See Section 4.2 Dose and Method of Administration, Paediatric.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Urinary alkalinisers such as acetazolamide and sodium bicarbonate increases blood quinine levels by decreasing renal clearance of quinine.

Urinary acidifiers such as ammonium chloride and some other drugs, decrease the pH of the urine and therefore increase the excretion of quinine, resulting in lower quinine blood levels.

Cimetidine: If used concurrently, it may reduce the clearance of quinine.

Digoxin: If used concurrently, it may result in increased serum digoxin concentrations and increased digoxin effect. Serum digoxin concentrations should be monitored and dosage adjustments made when necessary.

Anticoagulants: Hypoprothrombinaemic effects may be increased when quinine is used with warfarin, coumarin, or indanedione derivatives.

Pyrimethamine: Antimalarials such as this drug may displace quinine from protein binding sites resulting in excessive free quinine levels and possible toxicity.

Neuromuscular blocking agents: Including pancuronium bromide, atracurium besylate, suxamethonium chloride, mivacurium chloride, pipecuronium bromide, rapacuronium bromide, alcuronium chloride, cisatracurium besylate, doxacurium chloride, gallamine triethiodide, metocurine iodide, decamethonium bromide or diiodide,

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rocuronium bromide, vecuronium chloride and tubocurarine chloride are known to or may interact with quinine causing respiratory difficulties.

Agents which add to an enhancement of neuromuscular blocking drugs must be monitored with concurrent usage. These include:

Antiarrhythmics: Lignocaine, procainamide, quinidine, nifedipine and verapamil which all have neuromuscular blocking activity and may exacerbate neuromuscular block.

Anticholinesterases: Neostigmine and edrophonium may enhance neuromuscular block.

Diuretics: Frusemide and mannitol.

Antineoplastics: Caution should be used with anti-oestrogenic drugs such as tamoxifen.

Antibacterials: Some antibacterials in high concentration may produce a muscle paralysis which may be additive to or synergistic with that produced by neuromuscular blockers. This may be enhanced in patients with intracellular potassium deficiency or low plasma calcium concentration following large doses or renal impairment. The agents most commonly implicated are: aminoglycosides, lincosamides, polymixins, vancomycin and rarely, tetracyclines. These should be used with care with quinine or monitored very closely.

Calcium-channel blockers: Nifedipine and verapamil enhance the effect of neuromuscular blockade.

Ganglion blockers: Prolonged neuromuscular blockade has been reported in patients receiving neuromuscular blockers and trimetaphan.

General anaesthetics: Neuromuscular blockers are potentiated in a dose dependent manner by inhalation anaesthetics especially with competitive blockers. The greatest potentiation is from isoflurane, enflurane, desflurane and sevoflurane followed by halothane and cyclopropane.

Magnesium salts: Parenteral magnesium salts may potentiate the effects of neuromuscular blockade.

Sympathomimetics (Salbutamol): Intravenous salbutamol has been reported to enhance the blockade obtained with pancuronium and vecuronium.

Other: Antimyasthenics, haemolytics, neurotoxic medication, ototoxic medication, mefloquine, lithium and quinidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

The use of anti-malarials for the treatment of life threatening malaria during pregnancy is acceptable, because the small risk to the fetus is outweighed by the benefits to the mother and fetus. In high doses, quinine causes fetal injuries in the form of deafness, development disturbances, and malformation of the extremities and cranium. It has the ability to induce uterine contractions and constitutes a risk of abortion.

Use in lactation

Quinine is excreted in breast milk in small concentrations and caution should be exercised during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

When quinine is given repeatedly, a group of symptoms known as cinchonism occurs. Cinchonism symptoms include tinnitus, impaired hearing, headache, nausea, disturbed vision, vomiting, abdominal pain, diarrhoea, and vertigo.

Haematological: Acute haemolysis, thrombocytopenic purpura, agranulocytosis, and hypoprothrombinaemia.

CNS: Visual disturbances, blurred vision with scotomata, photophobia, diplopia, mydriasis, constricted visual fields, night blindness and disturbed colour perception. In severe cases the following adverse effects may also occur: tinnitus, vertigo, deafness, headache, confusion, syncope and optic atrophy (which may result in blindness).

Dermatological: Rashes, urticaria, pruritus, flushing of the skin, oedema of the face, photosensitivity.

Respiratory: Asthma precipitation.

Cardiovascular: Disturbance in cardiac rhythm on conduction, widening of the QRS complex, hypotension, ventricular tachycardia, angio-oedema, and angina symptoms in sensitive patients. Severe or even fatal cardiovascular toxicity can result from rapid intravenous administration of quinine.

Gastrointestinal: Nausea, vomiting, epigastric pain.

Musculo-skeletal: It may aggravate myasthenia gravis.

Hepatic: Hepatotoxicity.

Renal: Anuria, uraemia, haemoglobinuria (rarely).

Hypoglycaemia: It may aggravate hypoglycaemia. **Quinine may cause thrombocytopenia which may be fatal.**

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The exact mechanism of action of quinine in malaria is uncertain, but its actions appear to interfere with the function of plasmodial DNA. It inhibits protein synthesis by preventing strand separation and therefore DNA replication and transcription to RNA. Its primary action is schizonticidal, and no lethal effect is exerted on sporozoites or pre-erythrocytic tissue forms. It is gametocytocidal for *P. vivax* and *P. malariae*.

CNS: Quinine has slight analgesic and antipyretic activity. It has indifferent action on fevers except malarial fever.

Cardiovascular: The central action of quinine and its isomer quinidine on cardiac muscle, are qualitatively similar. However, normal therapeutic doses have small effect on normal cardiovascular systems. Toxic doses may cause myocardial depression and vasodilatation.

Smooth Muscle: Quinine has a slight oxytocic action on the gravid uterus. The spleen may contract by action on the musculature of its capsule, thus producing a lymphocytosis.

Skeletal Muscle: Quinine has a dual action on skeletal muscle. It acts directly on muscle fibres, increasing the tension response and refractory period. It can have a curare-like effect on skeletal muscle.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

No data available.

Distribution

The pharmacokinetics are altered significantly by malarial infection, the major effect being reduction in both its apparent volumes of distribution and its clearance.

Metabolism

Quinine is metabolised in the liver and rapidly excreted mainly in the urine.

Excretion

Excretion is increased in acid urine and decreased in alkaline urine.

Plasma protein binding is about 70% in healthy subjects, and rises to about 90% or more in patients with malaria. The elimination half-life in healthy patients is 11 hours but may be prolonged in patients with malaria. This suggests that during malaria there is impaired hepatic metabolism of quinine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No available data.

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Carcinogenicity

No available data.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Water for injections. It contains no antimicrobial preservative.

6.2 INCOMPATIBILITIES

Incompatible with amiodarone, pancuronium bromide, atracurium besylate, suxamethonium chloride, mivacurium chloride, pipecuronium bromide, rapacuronium bromide, alcuronium chloride, cisatracurium besylate, doxacurium chloride, gallamine triethiodide, metocurine iodide, decamethonium bromide or diiodide, rocuronium bromide, vecuronium chloride and tubocurarine chloride, diuretics especially frusemide, mannitol, heparin, intravenous ketamine.

Also see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions and Section 4.4 Special Warnings and Precautions for Use.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)¹. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mL vial supplied in a carton containing of 10 vials.

Phebra product code - INJ043

10 mL vial supplied in a carton containing 5 vials.

Phebra product code - INJ209

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: (8S, 9R)-6'-methoxycinchonan-9-ol dihydrochloride.

¹ AUST R 23101

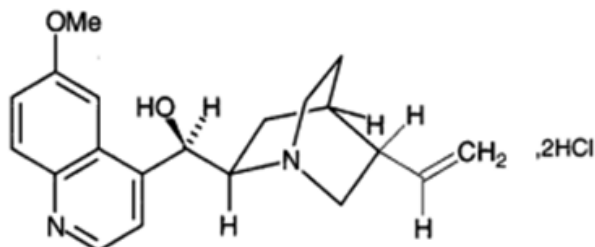
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The molecular weight of the compound is 397.3. The molecular formula is $C_{20}H_{24}N_2O_2 \cdot 2HCl$.

Chemical structure



CAS number

60-93-5.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4- PRESCRIPTION ONLY MEDICINE.

8 SPONSOR

Phebra² Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

14 Oct 1991

10 DATE OF REVISION

11 Feb 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformatted to align with new form with minor editorial changes.
1	Update active ingredient as per AAN
2	Minor Editorial change
3	Minor Editorial change
4.1	Minor editorial change to align with product name
4.5	Typographical correction from 'biiodatum' to 'diiodide'.
6.2	Typographical correction from 'biiodatum' to 'diiodide'.
7	Minor formatting change.

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