1. **Product Name**

Q300 300 mg film coated tablets.

2. **Qualitative and Quantitative Composition**

Each Q300 film coated tablet contains 300 mg of quinine sulfate.

Q300 contains lactose. For the full list of excipients, see section 6.1.

3. **Pharmaceutical Form**

Q300 film coated tablets are a clear film coated white biconvex tablet, 7/16" diameter, imprinted Q300 on one side.

4. **Clinical Particulars**

4.1 **Therapeutic indications**

Quinine is indicated concurrently with tetracycline or clindamycin or pyrimethamine plus sulphadiazine or sulphadoxine in the treatment of chloroquine-resistant malaria caused by *Plasmodium falciparum*.

Quinine is indicated in the treatment of myotonia.

4.2 **Dose and method of administration**

**Dose**

*Usual adult and adolescent dose*

**Malaria**

For chloroquine-resistant *Plasmodium falciparum* malaria:

Oral, 600 to 650 mg every eight hours for at least three days in most areas of the world (seven days in Southeast Asia) with concurrent or consecutive administration of 250 mg of tetracycline every six hours for seven days; or concurrent administration of 1.5 g of sulfadoxine and 75 mg of pyrimethamine combination as a single dose; or concurrent or consecutive administration of 900 mg of clindamycin three times a day for three days.

**Antimyotonic**

Oral, 300 to 650 mg two or three times a day.
Special populations

Paediatric

Malaria

For chloroquine-resistant *Plasmodium falciparum* malaria:

Oral, 8.3 mg per kg of body weight every eight hours for at least three days in most areas of the world (seven days in Southeast Asia) with concurrent or consecutive administration of 5 mg per kg of body weight of tetracycline every six hours for seven days in children over 8 years of age; or concurrent or consecutive administration of 6.7 to 13.3 mg per kg of body weight of clindamycin three times a day for three days; or concurrent administration of 1.25 mg per kg of body weight of pyrimethamine in combination with 25 mg per kg of body weight of sulfadoxine as a single dose.

Antimyotonic

Dosage has not been established.

Method of administration

Q300 may be taken with or after meals to minimise gastrointestinal irritation.

4.3 Contraindications

Quinine is contraindicated in patients with a history of hypersensitivity to quinine or to any of the excipients listed in section 6.1, in the presence of haemolysis, and in patients with tinnitus or optic neuritis. It should be used with caution in patients with atrial fibrillation or other serious heart disease. Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants. Quinine may aggravate the symptoms of myasthenia gravis and should be used with care if at all in such patients.

Pregnancy in a patient with malaria is not generally regarded as a contraindication to the use of quinine. Risk-benefit should be considered when the following medical problems exist:

- a history of Blackwater fever
- glucose-6-phosphate dehydrogenase (G6PD) deficiency hypoglycaemia

4.4 Special warnings and precautions for use

Quinine should be used with caution in patients with atrial fibrillation, conduction defects and heart block or other serious heart disease. It may cause hypoprothrombinaemia. Quinine should be avoided in patients with myasthenia gravis as it may aggravate their condition and cause severe respiratory distress and dysphasia.

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.

The administration of quinine to a patient who has previously been suffering from a chronic and inadequately controlled malarial infection may precipitate an attack of blackwater 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 an at increased risk of haemolytic anaemia during quinine therapy.

Quinine should not be withheld from pregnant women who have life threatening malaria (see section 4.6).

Treatment should be monitored in all patients in case signs of resistance develop.

Quinine can affect the results of certain urine tests for alkaloids and steroids. It may also interfere with tests for plasma catecholamines as well as slowing the erythrocyte sedimentation rate.
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. Such symptoms include tinnitus, impaired hearing, headache, nausea and disturbed vision (see sections 4.8 and 4.9).

Patients hypersensitive to quinidine may be hypersensitive to this medication also. 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.

Q300 film coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

**Paediatric use**

Appropriate studies with quinine for use as an antimyotonic have not been performed in the paediatric population. Antimalarial studies performed to date have shown that children have a decreased elimination half-life and volume of distribution; however, paediatrics-specific problems that would limit the usefulness of quinine in children have not been documented.

### 4.5 Interaction with other medicines and other forms of interaction

The following drug interactions have been noted with quinine sulfate. Combinations containing any of the following medications depending on the amount present may also interact with quinine sulfate.

**Effect of other medicines on quinine**

Quinine is metabolised via hepatic oxidative cytochrome P450 pathways, predominantly by CYP3A4. 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 CYP3A4 substrates, especially those causing prolongation of the QT interval.

**Effect of quinine on other medicines**

The plasma concentration of mefloquine may be increased.

Amantadine: quinine can reduce the renal clearance of amantadine.

If quinine is administered the maintenance dose of digoxin should be halved.

Ciclosporin: quinine can decrease serum 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.

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. Quinine has been reported to increase serum digoxin concentrations and quinine has
reduced total body clearance of digoxin. Quinine sulfate has been observed to interfere with Urinary 17-ketogenic steroid determinations.

**Other drug interactions**

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

There is an increased risk of ventricular arrhythmias with other drugs which prolong the QT interval, including amiodarone, moxifloxacin, pimozide, thioridazine and halofantrine, and therefore concomitant use with these products should be avoided.

Antiarrhythmics: Concomitant use of amiodarone should be avoided due to the increased risk of ventricular arrhythmias. The plasma concentration of flecainide is increased by quinine.

Quinidine: 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. In one report, reductions in warfarin dosage were necessary after ingestion of large amount of tonic water containing quinine.

Antihistamines: Concomitant use of terfenadine should be avoided due to the increased risk of ventricular arrhythmias.

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.

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.

Suxamethonium: Quinine enhances the neuromuscular effects of suxamethonium.

Ulcer-healing drugs: Cimetidine inhibits quinine metabolism leading to increased plasma-quinine concentrations.

Concomitant use of artemether and lumefantrine should be avoided.

### 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 sulfate should not be used during pregnancy unless the benefits outweigh the risks.

Pregnancy in a patient with malaria is not generally regarded as a contraindication 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.

**Breast-feeding**

Quinine sulfate is excreted in breast milk, but no problems in humans have been reported. However, quinine sulfate should not be given to nursing mothers unless the benefits outweigh the risks.
Fertility
No data available.

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
Cinchoanism 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. Its more serious manifestation 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, hypoprophorbinemia, hemoglobinuria, oliguria, hemolytic-uremic 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, 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 and death have been received.

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

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, dyspnoea may occur.

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

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

Musculoskeletal, connective tissue and bone disorders: muscle weakness may occur, aggravation of Myasthenia gravis.

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.

General disorders and administration site conditions: Fever
Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions [https://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/).

4.9 Overdose

Quinine overdosage may lead to serious and irreversible side effects including irreversible visual loss and can be fatal. In acute overdosage, symptoms of cinchonism may occur, including convulsions, nausea, vomiting, tinnitus, deafness, headache, vasodilatation and disturbed vision. Features of a significant overdose include convulsions, impairment of consciousness, coma, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. Fatalities have been reported in adults after doses of 2-8 g. High doses of quinine are teratogenic and may cause miscarriage.

The effects of oculotoxicity may include blurred vision, defective colour perception, visual field constriction and total blindness. The onset of symptoms may vary from a few hours to a day or more after ingestion. Visual disturbances are usually slowly reversible but there may be residual damage.

The effects associated with cardiovascular toxicity include conduction abnormalities, ventricular dysrhythmias, anginal symptoms and hypotension leading to cardiac arrest and circulatory failure. 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.

Quinine is rapidly absorbed. In patients who present within one hour of ingestion an overdose gastric lavage may be considered, but the risk of aspiration must be considered, especially if there is CNS depression or drowsiness. Multiple doses of activated charcoal may be considered.

Observe patients for at least 12 hours after ingestion. Monitor cardiac conduction and rhythm, serum electrolytes, blood glucose and visual acuity.

Other treatment is mostly symptomatic to maintain blood pressure, respiration, renal function and treating arrhythmia, convulsions, hypoglycaemia and acidosis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, ATC code: P01BC01

Mechanism of action

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.
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.

The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite.

Quinine increases the refractory period of muscle so that the tetanic stimulation is diminished. It also affects a number of other body systems including the central nervous system, the cardiovascular system, the gastrointestinal tract and the pancreas. In addition, quinine exhibits local anaesthetic action and a local irritant action. As an antimalarial drug it acts primarily as a schizontocide. It is more toxic and less effective than chloroquine, but is especially useful for treatment of chloroquine-resistant strains of malarial infection.

5.2 Pharmacokinetic properties

Absorption
Quinine is rapidly and almost completely absorbed from the gastrointestinal tract. Peak concentrations in the circulation are attained about 1 to 3 hours after ingestion.

Distribution
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 to 7% of those in the plasma.

Quinine crosses the placenta and is excreted in the breast milk.

Biotransformation
Quinine is extensively metabolised in the liver and rapidly excreted in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5% to 20%.

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.

The pharmacokinetics of quinine are altered significantly by malaria infection, with reductions in both the apparent volume of distribution and clearance.

6. Pharmaceutical Particulars

6.1 List of excipients
Each Q300 film coated tablet contains 300 mg of active ingredient, quinine sulfate. It also contains:
- lactose
- magnesium stearate
- povidone
- sodium starch glycollate
- ethanol

The film coating contains
- ethanol
- diethyl phthalate
• purified water
• hypromellose
• carnauba wax.

Q300 is gluten free.

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years.

6.4 **Special precautions for storage**
Store at or below 25°C. Protect from light.

6.5 **Nature and contents of container**
HDPE bottle with PP cap. Pack size of 500 tablets.

6.6 **Special precautions for disposal**
Not applicable.

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7. **Medicines Schedule**

Prescription Medicine

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8. **Sponsor Details**

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

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9. **Date of First Approval**

6 March 1980

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10. **Date of Revision of the Text**

21 November 2018

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<td>Additional cardiovascular, glucose-6-phosphate dehydrogenase deficiency and pregnancy precautions added. Steven-Johnson syndrome added to hypersensitivity reaction warning. Additional information regarding thrombocytopenia added.</td>
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