BRAND NAME:	**OSYQUINE TABLETS**
GENERIC NAME:	**QUININE SULFATE TABLET BP 300MG**

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Enclosed

BRAND NAME:	**OSYQUINE TABLETS**
GENERIC NAME:	**QUININE SULFATE TABLET BP 300MG**

1. Name of drug product

OSYQUINE TABLETS

1.1 (Trade) name of product

OSYQUINE TABLET

(Quinine Sulfate Tablet BP 300 mg)

1.2 Strength

Quinine Sulfate 300 mg

1.3 Pharmaceutical Dosage Form

Oral dosage form **(**Tablets)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each Sugar coated Tablet Contains:

Quinine Sulfate BP …….300 mg

Excipients …….q.s.

Colour : Indigo Carmine

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Batch Formula:

Batch Size: 352.200 Kg ≅ 6,00,000 Tablets

Sr. No.	Ingredients	Spec	Unit Formula (mg)	Batch Formula (kg)
GRANULATION				
DRY MIXING				
1	Quinine Sulfate	BP	300.00	180.000*
2	Dicalcium Phosphate	BP	22.000	13.200
3	Maize Starch	BP	21.500	12.900**
BINDER				
4	Maize Starch	BP	17.700	10.620
5	PVP K-30	BP	10.000	6.000
6	Sodium Benzoate	BP	1.000	0.600
7	Purified water	IH	q.s.	33.000
LUBRICATION				
8	Purified Talc	BP	8.800	5.280
9	Sodium Starch Glycolate	BP	20.000	12.000
10	Maize Starch	BP	-	2.352***
11	Magnesium Stearate	BP	4.000	2.400
Weigh of Compressed Tablet			**405.0 mg**	**243.000 kg**
COATING				
DUSTING				
12	Calcium Carbonate	IH	20.000	12.000
13	Purified water	BP	20.000	12.000
DUSTING SOLUTION				
14	Sugar (pharma grade sugar)	IH	42.820	28.260@
15	Gelatin	BP	2.000	1.200
16	Methyl Paraben	IH	0.060	0.036
17	Propyl paraben	BP	0.030	0.018
18	Purified water	IH	q. s.	7.800
SMOOTHING SOLUTION				
19	Sugar (pharma grade sugar)	IH	31.500	20.790@
20	Purified water	IH	q. s.	7.900
21	Gelatin	BP	0.500	0.300
22	Methyl Paraben	IH	0.060	0.036
23	Propyl Paraben	BP	0.030	0.018
24	Titanium Dioxide	IH	2.400	1.440
25	Calcium Carbonate	IH	4.800	2.880
PLAIN SOLUTION				

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26	Sugar (Pharma grade sugar)	IH	48.000	31.680@
27	Purified Water	IH	q.s	3.400
28	Titanium Dioxide	IH	9.000	5.400
POLISHING				
29	Isopropyl Alcohol	BP	q.s	10.200
30	Bees Wax	BP	0.400	0.240
31	Carnuba Wax	IH	0.400	0.240
Weight gain of Sugar Coating Stage			**182.0 mg**	**243.000 kg**
Weight of Sugar Coated tablet			**587.0 mg**	**352.200 kg**

Remark:

Quantity of Quinine sulfate are taken after calculation based on assay.

**Maize starch changes according to change in quantity of Quinine sulfate.

****10%extra Maize starch dried added to compensate loss of moisture from starch quantity during drying process.

@ 10% Extra sugar added to compensate process loss in coating.

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3. PHARMACEUTICAL DOSAGE FORM

Tablets

White circular, biconvex uncoated tablet, plain on both side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1) Treatment of falciparum (malignant tertian) malaria.

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

4.2 Posology and method of administration

Posology

Posology

For the treatment of falciparum (malignant tertian) malaria:

Adults (including elderly) and children aged 12 years and over: 600mg every eight hours for 7 days. The dose may depend upon the size of the patient, severity of infection, and evidence of renal or liver disease (when the intervals should be increased), due to a prolonged half-life of the drug.

If quinine resistance is known or suspected on completion of the course additional treatment may be given. This may be one of the following:

1.Doxycycline 200mg daily (as a single dose or in 2 divided doses) for at least 7 days.

2.Clindamycin 300mg four times daily for 5 days.

Children aged 10-12 years: 10mg/kg every eight hours for 7 days.

Children under 10 years: Not recommended

For the treatment and prevention of nocturnal leg cramps:

Adults (including elderly):

The recommended dose is 200mg at bedtime. The maximum dose is 300mg.

A reduction in frequency of leg cramps may take up to 4 weeks to become apparent. Patients

should be monitored closely during the early stages of treatment for adverse effects. After an initial trial of 4 weeks, treatment should be stopped if there is no benefit. Treatment should be interrupted at approximately three monthly intervals to assess the need for continuation of treatment with quinine.

Method of Administration

For oral administration.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• Haemolysis or Haemoglobinuria

• Optic neuritis

• Tinnitus

• Myasthenia gravis, quinine may cause severe respiratory distress and dysphagia in these patients.

• As quinine has been implicated in precipitating blackwater fever, it is generally contraindicated in patients who have already suffered an attack.

4.4 Special warnings and precautions for use

Cinochonism

• 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.

Hypersensitivity

• 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.

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Cardiac disorders

• 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. 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.

Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency

• Quinine has been implicated in precipitating blackwater 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.Quinine should not be withheld from pregnant women who have life threatening malaria.

• Treatment with quinine should be monitored in case signs of resistance develop.

• 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 sulfate 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.

• Reduce the dosage (or increase intervals between doses) in renal or hepatic disease.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs 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.

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

Quinine may increase the levels of phenobarbital and of carbamazepine. Patients should be monitored closely during concomitant use of quinine with these agents.

Effect of Quinine on other drugs

The plasma concentration of flecanide, digoxin and mefloquine may be increased.

Amantadine: Quinine can reduce the renal clearance of amantadine with risk of amantadine toxicity (including headache, nausea, dizziness).

Analgesics: increased risk of ventricular arrhythmias with levacetylmethadol (avoid concomitant use).

Ciclosporin: Quinine can decrease serum plasma concentrations of ciclosporin.

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.

Other drug interactions

There is an increased risk of ventricular arrhythmias with other drugs which prolong the QT interval, including amiodarone, moxifloxacin, pimozide, thioridzine and halofantrine.

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.

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 reduced the serum levels of quinine, therefore reducing its therapeutic effect.

Anticoagulants: Quinine may cause hypoprothrombinaemia and enhance the effects of anticoagulants.

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

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

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: There is an increased risk of ventricular arrhythmias and concomitant use should be avoided with pimozide or thioridazine.

Hypoglycaemics: There is an increased risk of hypoglycaemia when taken concurrently.

Suxamethonium: Quinine enhances the neuromuscular effects of suxamethonium.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Large doses of quinine can induce abortion. 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.

Treatment of falciparium malaria: 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.

Prophylaxis of nocturnal leg-cramps: Quinine sulfate should not be used during pregnancy to treat cramps.

Breastfeeding

Quinine sulfate 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 sulfate should not be given to nursing mothers unless the benefits outweigh 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

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reaction
	Frequency
	Not Known
Blood and lymphatic system disorders	Thrombocytopenia, intravascular coagulation, hypoprothrombinaemia, haemoglobinuria, haemolytic-uremic syndrome, pancytopenia, haemolysis agranulocytosis,thrombocytopenic purpura.

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Immune system disorder.	Eczematous dermatitis, oedema, erythema, lichen planus, hypersensitivity reactions (asthma, angioneurotic oedema, photosensitivity, hot and flushed skin, fever, pruritis, thrombocytopenic purpura and urticaria).
Metabolism and nutrition disorders	Hypoglycaemia.
Psychiatric disorders	Agitation, confusion.
Nervous system disorders	Headache, vertigo, excitement, loss of consciousness, coma, death.
Eye disorders	Blurred vision, defective colour perception, visual field constriction.
Ear and labyrinth disorders	Tinnitus, impaired hearing.
Cardiac disorders	Atrioventricular conduction disturbances, a fall in blood pressure coupled with a feeble pulse, prolongation of the QT interval, widening of the QRS complex, T wave flattening.
Respiratory, thoracic and mediastinal disorders Gastrointestinal disorders	Bronchospasm, dyspnoea.
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain*.
Skin and subcutaneous tissue disorders	Flushing, rash, urticaria, eczematous dermatitis, oedema, erythema, lichen planus, pruritis, photosensitivity , Stevens-Johnson syndrome.
Musculoskeletal and connective tissue disorders	Muscle weakness, aggravation of Myasthenia gravis
Renal and urinary disorders	Renal insufficiency, acute renal failure (may be due to an immune mechanism or to circulatory failure), oliguria
Reproductive system and breast disorders	Abortion**
General disorders and administration site conditions	Cinchonism***

May occur after long term administration of quinine.

** Toxic doses of quinine may induce abortion, but it is unwise to withhold the drug if less toxic antimalarials are not available.

*** 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 severe manifestations symptoms may include gastrointestinal symptoms, oculotoxicity, CNS disturbances, cardiotoxicity and death. Visual disorders (blurred vision, defective colour perception, visual field constriction and total blindness).

4.9 Overdose

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

Features of a significant teratogenic and may cause miscarriage. Hypokalaemia and hypoglycaemia may also occur.

The overdose include convulsions, impairment of consciousness, respiratory depression, QT prolongation, ventricular arrhythmia, cardiogenic shock and renal failure. High doses of quinine are

reatment: 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 200 mg tablet is equivalent to 165 mg quinine base, 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.

5.0 Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherpeutic group: Quinine alkaloid.

ATC Code: P01B C01.

Pharmacodynamics effect

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.

Mechanism of action

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

5.2 Pharmacokinetic properties

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

Absorption:

Quinine is rapidly and almost completely absorbed from the GI tract and peak concentrations in the circulation are attained about 1-3 hours after oral administration of the sulfate.

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 2-7% of those in the plasma.

Biotransformation

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

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

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.

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

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical Particulars

6.1. List of excipients

Maize Starch

Sodium Benzoate

PVP K-30

Sodium Starch Glycolate

Magnesium Stearate

Calcium carbonate

Purified Talc

Sugar

Gelatin

Methyl Paraben

Propy paraben

Titanium Dioxide

Isopropyl Alcohol Bees Wax

Carnauba Wax

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6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store below 30^0C. Protect from light.

Keep all medicines out of reach of children.

6.5. Nature and contents of container

10 X 10 Tablets packed in Alu-PVC Blister.

6.6. Instruction for use and handling

No special requirement

7. Marketing Authorization Holder

MAXHEAL LABORATORIES PVT LTD

PLOT NO. - 2-7/80-85, SURSEZ,

G.I.D.C SACHIN, SURAT

GUJARAT-394230. INDIA

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization /Renewal of the Authorization

Not Applicable.

10. Date of Revision of the

Not Applicable.