For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

HQTOR

1. Generic Name

Hydroxychloroquine Sulphate Tablets I.P.

2. Qualitative and quantitative composition

HQTOR 200

Each film coated tablet contains:

Hydroxychloroquine Sulphate I.P. ……200 mg

Excipients……...q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Maize Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Purified Talc, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol, Triacetin, Tribasic Calcium Phosphate and Titanium Dioxide.

HQTOR 400

Each film coated tablet contains:

Hydroxychloroquine Sulphate I.P. ……400 mg

Excipients……...q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Maize Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Purified Talc, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate Polyvinyl Alcohol, Polyethylene Glycol, Triacetin, Tribasic Calcium Phosphate and Titanium Dioxide.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: Hydroxychloroquine Sulphate - 200mg and 400mg.

4. Clinical particulars

4.1 Therapeutic indication

200mg

It is indicated for treatment of acute or chronic rheumatoid arthritis in adult patients and for the treatment of systemic lupus erythematosus.

400mg

It is indicated for treatment of acute or chronic rheumatoid arthritis in adult patients and for the treatment of systemic lupus erythematosus.

As an adjunct to diet and exercise to improve glycemic control of patients on metformin, sulfonylurea combination in patients with Type II Diabetes.

4.2 Posology and method of administration

Dosing Considerations: Absolute body weight used as a guide to dosage could result in an overdosage; daily doses should not exceed 6.5 mg (salt form)/kg ideal (lean) body weight. Exceeding the recommended daily dose sharply increase the risk of retinal toxicity as well as cardiac arrhythmias. The dosages cited below are stated in terms of hydroxychloroquine sulfate. One 200 mg tablet is equivalent to 155 mg base. Each dose should be taken with a meal or a glass of milk.

Recommended Dose and Dosage Adjustment:

Rheumatoid Arthritis:

The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur somewhat early. Several months of therapy may be required before maximum effects can be obtained. If objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months, the drug should be stopped. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial dosage – In adults, from 400 to 600 mg daily. In a few patients, the side effects may require temporary reduction of the initial dosage. Generally, after five to ten days the dose may be gradually increased to the optimum response level, frequently, without return of side effects.

Maintenance dosage – When a good response is obtained (usually in four to twelve weeks), the dosage is reduced by 50 percent and continued at an acceptable maintenance level of 200 to 400 mg daily. The incidence of retinopathy has been reported to be higher when the maintenance dose is exceeded. If a relapse occurs after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Use in Combination Therapy: HQTOR may be used safely and effectively in combination with corticosteroids, salicylates, NSAIDS, and methotrexate and other second line therapeutic agents. Corticosteroids and salicylates can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is suggested, it may be done by reducing every four to five days, the dose of cortisone by no more than 5 to 15 mg; of hydrocortisone from 5 to 10 mg; of prednisolone and prednisone from 1 to 2.5 mg; of methylprednisolone and triamcinolone from 1 to 2 mg and dexamethasone from 0.25 to 0.5 mg. Regimens of treatment using other agents than steroids and NSAIDS are under development. No definitive dose combinations have been established.

Lupus Erythematosus:

Initially, the average adult dose is 400 mg once or twice daily. This may be continued for several weeks or months, depending upon the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200 to 400 mg daily will suffice. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Diabetes mellitus:

As directed by the physician

Dosing in Special Populations:

Patients with Hepatic Impairment: HQTOR should be used with caution in patients with hepatic impairment; a reduction in dosage may be necessary.

Patients with Renal Impairment: HQTOR should be used with caution in patients with renal impairment; a reduction in dosage may be necessary.

4.3 Contraindications

HQTOR is contraindicated in:

– Patients with pre-existing retinopathy of the eye

– Patients with known hypersensitivity to 4-aminoquinoline compounds

– children below 6 years of age (200 mg tablets not adapted for weight < 35 kg).

4.4 Special warnings and precautions for use

General:

Observe caution in patients with gastrointestinal or neurological disorders, in those with sensitivity to quinine, and in porphyria.

Effects on Ability to Drive and Use Machinery: Patients should be warned about driving and operating machinery since HQTOR can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced.

Carcinogenesis and Mutagenesis:

Non-clinical studies showed a potential risk of chloroquine inducing gene mutations. Long term studies in animals have not been conducted to evaluate the carcinogenic potential. In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving-long term treatment.

Cardiomyopathy: Cases of cardiomyopathy resulting in cardiac failure, in some cases with a fatal outcome, have been reported in patients treated with HQTOR. HQTOR should be discontinued if signs and symptoms of cardiomyopathy develop. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrio-ventricular heart block) as well as biventricular hypertrophy is diagnosed. **Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias:** HQTOR can prolong the PR, QRS and QTc intervals, especially in patients with underlying risk factors. Serious adverse events, including fatal outcomes, have been reported in patients taking HQTOR including ventricular arrhythmias, heart blocks, ventricular fibrillation and torsade de pointes.

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Permanently discontinue HQTOR in patients who develop torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. If cardiac complications due to HQTOR are suspected, treatment should be discontinued. HQTOR is not recommended for use in patients with baseline QTc prolongation (e.g., congenital or acquired Long QT Syndrome), second-or third-degree atrioventricular block. Electrolyte imbalances (e.g. hypokalemia/hypomagnesemia/hypocalcemia) must be

corrected prior to use. Use of HQTOR should be undertaken with extreme caution in patients with other risk factors for torsade de pointes.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥ 65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Concomitant use with other QTc, PR or QRS interval prolonging drugs should be avoided or undertaken with particular caution.

The magnitude of QT, PR or QRS prolongation with HQTOR may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

Endocrine and Metabolism:

HQTOR has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with HQTOR should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with HQTOR should have their blood glucose level checked and the need for HQTOR treatment reviewed as necessary. In cases of severe hypoglycemia, HQTOR should be discontinued and alternative therapy considered. If patients use HQTOR concomitantly with antidiabetic drugs, a decrease in doses of insulin or antidiabetic drugs may be required as HQTOR may enhance the effects of hypoglycemic treatment.

Hematologic:

Periodic blood counts should be obtained in patients requiring prolonged therapy due to the risk of bone marrow depression. If any severe blood disorder appears that is not attributable to the disease under treatment, the drug should be discontinued.

Observe caution in patients with blood disorders or glucose-6-phosphate dehydrogenase deficiency.

Hepatic/Biliary/Pancreatic:

HQTOR should be used with caution in patients with hepatic disease or alcoholism, in whom a reduction in dosage may be necessary, or in conjunction with known hepatotoxic drugs.

Use of HQTOR in patients with hepatic impairment as well as with concomitant CYP2C8 or CYP3A4 inhibitors can result in elevation of hydroxychloroquine plasma concentrations, with the magnitude of the effect depending on the degree of hepatic impairment, as well as the enzyme inhibited and the potency of the inhibitor. Isolated cases of abnormal liver function tests as well as fulminant hepatic failure have been reported.

Musculoskeletal:

All patients on long term therapy with this preparation should be questioned and examined periodically, including the examination of skeletal muscle function and tendon reflexes, testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

Neurologic:

Extrapyramidal reactions have been reported in patients taking HQTOR. Symptoms may persist in some patients after discontinuation of therapy.

Ophthalmologic:

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Before starting a long term treatment, both eyes should be examined by careful ophthalmoscopy for visual acuity, central visual field and colour vision, and fundoscopy. Then, the examination should be repeated at least annually.

Retinal toxicity is largely dose-related. The risk of retinal damages is small with daily doses of up to 6.5 mg/kg ideal (lean) body weight. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity. Significant risk factors for toxic retinopathy reported during long-term (≥5 years) treatment with hydroxychloroquine include daily doses greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, subnormal glomerular filtration rate, durations of use longer than five years, and concurrent treatment with tamoxifen citrate. Concomitant use of HQTOR with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

Careful ophthalmologic examination should be more frequent and adapted to the patient, in the following situations:

- Daily doses exceeding 6.5 mg (salt form)/kg ideal (lean) body weight. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese;

- Renal insufficiency;

- Cumulative dose more than 200 g (salt form);

- Elderly;

- impaired visual acuity.

If there is any indication of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks, abnormal colour vision) that are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be stopped immediately. The patient should be closely observed for possible progression of the abnormality. Retinal changes (and visual disturbances) may progress even after cessation of the therapy.

Methods recommended for early diagnosis of retinopathy consist of

(1) funduscopic examination of the macula for fine pigmentary disturbances or loss of the foveal reflex and

(2) examination of the central visual field with a small red test object for pericentral or paracentral scotoma or determination of retinal thresholds to red. Any unexplained

visual symptoms, such as light flashes or streaks also should be regarded with suspicion as possible manifestations of retinopathy.

Psychiatric:

Suicidal behaviour has been reported in patients treated with HQTOR.

Renal:

Observe caution in patients with renal disease, in whom a reduction in dosage may be necessary, as well as in those taking medicines known to affect this organ. During treatment and after discontinuation, monitoring for adverse reactions may be warranted in patients with severe renal impairment or end-stage renal disease (ESRD), given the long half-life of hydroxychloroquine.

Skin:

Dermatological reactions to HQTOR may occur. It is not recommended for the treatment of psoriasis or porphyria as these conditions may be exacerbated by its use. Observe caution in patients with psoriasis.

HQTOR may cause acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although HQTOR may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favorable after discontinuation of drug.

Sexual Health:

Fertility:

Animal studies showed an impairment of male fertility with chloroquine treatment. There are no data in humans.

Special Populations

Pregnancy:

Hydroxychloroquine crosses the placenta. Data are limited regarding the use of HQTOR during pregnancy. HQTOR should be avoided in pregnancy. It should be noted that the 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation to the foetus.

Embryonic deaths and ocular malformations in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers:

Careful consideration should be given to using HQTOR during breastfeeding, since it is excreted in small amounts (approximately 2% of the maternal dose after bodyweight correction) in human breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines. There are very limited data on the safety in the breastfed infant during hydroxychloroquine long-term treatment. The prescriber should assess the potential risks and benefits of use during breastfeeding, according to the indication and duration of treatment.

Although hydroxychloroquine is excreted in breast milk, the amount is insufficient to confer any protection against malaria to the infant. Separate chemoprophylaxis for the infant is required.

Pediatric Use:

Safety and efficacy has not been established in rheumatoid arthritis or systemic lupus erythematosus in children. Children are especially sensitive to the 4-aminoquinoline compounds. The most reported fatalities follow the accidental ingestion of chloroquine, sometimes in small doses. Patients should be strongly warned to keep these drugs out of the reach of children.

Hepatic Impairment:

HQTOR should be used with caution in patients with hepatic disease or alcoholism, in whom a reduction in dosage may be necessary, or in conjunction with known hepatotoxic drugs. Isolated cases of abnormal liver function tests as well as fulminant hepatic failure have been reported.

Renal Impairment:

HQTOR should be used with caution in patients with renal disease, in whom a reduction in dosage may be necessary, as well as in those taking medicines known to affect this organ.

Monitoring and Laboratory Tests

ECG assessments are recommended at baseline and periodically during treatment with HQTOR. More frequent monitoring is recommended if HQTOR is administered to patients with baseline ECG abnormalities or who are being treated concomitantly with other QTc-, QRS-, or PR-interval prolonging drugs. Monitor electrolytes regularly.

4.5 Drugs interactions

Drugs that Prolong the PR, QRS and/or QTc Intervals:

HQTOR has the potential to prolong the PR, QRS and/or QTc intervals in a concentration-related manner. Caution is recommended if HQTOR is used concomitantly with other drugs that prolong the PR, QRS and QTc intervals. Current information sources should be consulted for drugs that prolong the QTc interval, the QRS duration, or the PR interval.

Drugs that Affect Electrolytes:

Caution is recommended if HQTOR is used with drugs that have the potential to decrease electrolytes levels. Current information sources should be consulted for drugs that disrupt electrolytes.

A table with potential drug interaction with HQTOR is included below. This list of possible drug interactions is not exhaustive. HQTOR should also be used with caution in patients taking medicines which may cause adverse ocular or skin reactions.

Proper Name	**Effect/clinical comment**
Agalsidase	There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when HQTOR is co-administered with agalsidase.
Aminoglycoside antibiotics	HQTOR may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including potentiation of

Proper Name	Effect/clinical comment
	its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics.
Antacids	As with chloroquine, antacids may reduce absorption of HQTOR so it is advised that a 4 hour interval be observed between HQTOR and antacid dosing.
Antidiabetic drugs	May enhance the effects of a hypoglycemic treatment, a decrease in doses of antidiabetic drugs may be required.
Antiepileptic drugs	The activity of antiepileptic drugs might be impaired if co-administered with HQTOR.
Antimalarials known to lower the convulsion threshold	HQTOR can lower the convulsive threshold. Co-administration of HQTOR with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.
Cimetidine	HQTOR may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including inhibition of its metabolism by cimetidine, which may increase plasma concentration of the antimalarial.
Cyclosporine	An increased plasma cyclosporine level was reported when cyclosporine and HQTOR were co-administered.
CYP2C8 and CYP3A4 inhibitors	Co-administration of HQTOR with moderate and strong CYP2C8 and CYP3A4 inhibitors (such as, but not limited to, ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir) may result in increased plasma concentrations of hydroxychloroquine.
Digoxin	May result in increased serum digoxin levels; serum digoxin levels should be closely monitored in patients receiving concomitant treatment.
Drugs that prolong the QRS and/or QT interval and other arrhythmogenic drugs	HQTOR prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. There may be an increased risk of inducing ventricular arrhythmias if HQTOR is used concomitantly with other drugs that prolong the QT interval, including, but not limited to, Class IA, IC and III antiarrhythmics; certain antidepressants, antipsychotics, and anti-infectives; domperidone; 5-hydroxytryptamine (5-HT)3 receptor antagonists; kinase inhibitors; histone deacetylase inhibitors beta-2 adrenoceptor agonists.
Drugs that affect electrolytes	Caution is recommended if HQTOR is used with drugs that have the potential to decrease electrolytes levels, including, but not limited to, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors.

Proper Name	Effect/clinical comment
Insulin	May enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin may be required
Mefloquine	HQTOR can lower the convulsive threshold. Co-administration of HQTOR with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.
Neostigmine	HQTOR may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared including antagonism of effect of neostigmine.
Praziquantel	Chloroquine has been reported to reduce the bioavailability of praziquantel. Due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for HQTOR
Pyridostigmine	HQTOR may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including antagonism of effect of pyridostigmine
Tamoxifen/Drugs known to induce retinal toxicity	An increased risk of toxic retinopathy was reported when HQTOR was used concurrently with tamoxifen citrate. Concomitant use of HQTOR with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.
Vaccine: Human diploid cell rabies vaccine	HQTOR may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including reduction of the antibody response to primary immunization with intradermal human diploid cell rabies vaccine.

Drug-Food Interactions: Grapefruit products contain one or more components that strongly inhibit CYP3A4 and can increase plasma concentrations of hydroxychloroquine. Consumption of grapefruit or its juice should be avoided while taking HQTOR.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Sexual Health:

Fertility:

Reported animal studies showed an impairment of male fertility with chloroquine treatment. There are no data in humans.

Special Populations

Pregnancy:

Hydroxychloroquine crosses the placenta. Data are limited regarding the use of HQTOR during pregnancy. HQTOR should be avoided in pregnancy. It should be noted that the 4-aminoquinolines in therapeutic doses have been associated with central nervous

system damage, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation to the foetus.

Embryonic deaths and ocular malformations in the offspring have been reported when pregnant rats received large doses of chloroquine.

Nursing Mothers:

Careful consideration should be given to using HQTOR during breastfeeding, since it is excreted in small amounts (approximately 2% of the maternal dose after body weight correction) in human breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines. There are very limited data on the safety in the breastfed infant during hydroxychloroquine long-term treatment. The prescriber should assess the potential risks and benefits of use during breastfeeding, according to the indication and duration of treatment.

Although hydroxychloroquine is excreted in breast milk, the amount is insufficient to confer any protection against malaria to the infant. Separate chemoprophylaxis for the infant is required.

4.7 Effects on ability to drive and use machines

Patients should be warned about driving and operating machinery since HQTOR (hydroxychloroquine sulfate tablets) can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced.

4.8 Undesirable effects

The following Council for International Organizations of Medical Sciences (CIOMS) frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and <0.1 %; Very rare < 0.01 %; Not known (frequency cannot be estimated from available data).

Blood and lymphatic system disorders

Not known: Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, and thrombocytopenia.

Cardiac disorders

Not known: Cardiomyopathy, which may result in cardiac failure and in some cases a fatal outcome.

Chronic toxicity should be considered when conduction disorders (bundle branch block/ atrioventricular heart block) as well as biventricular hypertrophy are found. Drug discontinuation may lead to recovery.

HQTOR prolongs the QT, PR and/or QRS intervals which may lead to an arrhythmia. Ventricular arrhythmias and torsade de pointes have been reported in patients taking HQTOR.

Ear and labyrinth disorders

Uncommon: Vertigo, tinnitus.

Not known: Hearing loss, including cases of irreversible hearing loss.

Eye disorders

Common: Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible.

Uncommon: Maculopathies, which may be irreversible.

Retinopathy with changes in pigmentation and visual field defects. In its early form it appears reversible upon discontinuation of the drug. If allowed to develop however, there may be a risk of progression even after treatment withdrawal.

Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, abnormal colour visions, reduction in visual acuity, night blindness, difficulty reading and skipping words.

Corneal changes including edema and opacities. They are either symptomless or may cause disturbances such as halos around lights especially at night, blurring of vision, vision disturbances, or photophobia. They may be transient or are reversible upon discontinuation of therapy.

Not known: Macular degeneration, which may be irreversible.

Gastrointestinal disorders

Very common: Abdominal pain, nausea.

Common: Diarrhea, vomiting.

These symptoms usually resolve immediately upon reducing the dose or upon stopping the treatment.

Hepatobiliary disorders

Uncommon: Abnormal liver function tests.

Not known: Fulminant hepatic failure.

Immune system disorders

Not known: Urticaria, angioedema, bronchospasm.

Metabolism and nutrition disorders

Common: Anorexia (usually resolves immediately upon reducing the dose or upon stopping the treatment).

Not known: hypoglycemia.

HQTOR may exacerbate porphyria.

Musculoskeletal and connective tissue disorders

Uncommon: Sensori motor disorders.

Not known: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Depression of tendon reflexes, abnormal results of nerve conduction tests. Myopathy may be reversible after drug discontinuation, but recovery may take many months.

Nervous system disorders

Common: Headache.

Uncommon: Dizziness.

Not known: Convulsions. Extrapyramidal reactions such as: akathisia, dystonia, dyskinesia, gait disturbance, tremor.

Psychiatric disorders

Common: Affect lability.

Uncommon: Nervousness.

Not known: Psychosis, suicidal behavior.

Skin and subcutaneous tissue disorders

Common: Skin rash, pruritus.

Uncommon: Pigmentary changes in skin and mucous membranes, bleaching of hair, alopecia. These usually resolve readily upon cessation of therapy.

Not known: Bullous eruptions (including urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum), toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), photosensitivity, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2 grams having proved fatal.

Symptoms:

The 4-aminoquinoline compounds are very rapidly and completely absorbed following ingestion and in accidental overdosage toxic symptoms may occur within 30 minutes. These consist of headache, drowsiness, visual disturbances, cardiovascular collapse, hypokalemia and convulsions, rhythm and conduction disorders, including QT interval prolongation, torsade de pointes, ventricular tachycardia, ventricular fibrillation, width-increased QRS complex, PR interval prolongation, bradyarrhythmias, nodal rhythm, atrioventricular block, followed by sudden potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after overdose.

In the event of acute overdose, the patient should be carefully observed (e.g., ECG monitoring) and given symptomatic and supportive treatment. The ECG may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Treatment:

Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital), or gastric lavage until the stomach is completely emptied. If finely powdered activated charcoal is introduced by the stomach tube, after lavage and within 30 minutes after ingestion of the tablets, it may inhibit further intestinal absorption of the drug. To be effective, the

dose of activated charcoal should be at least five times the estimated dose of ingested hydroxychloroquine. Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultrashort-acting barbiturate may be tried but, if due to anoxia, convulsions should be corrected by oxygen administration, artificial respiration or, in shock with hypotension, by vasopressor therapy. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, has also been advised. Exchange transfusions have been used to reduce the level of 4-aminoquiolines in the blood.

Consideration should be given to administering diazepam parenterally since studies have reported it beneficial in reversing chloroquine cardiotoxicity.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 hours. Fluids may be forced, and sufficient ammonium chloride may be administered for a few days to acidify the urine to help promote urinary excretion.

If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) three or four days a week be administered for several months after therapy has been stopped, as acidification of the urine increases renal excretion of the 4-aminoquinoline compounds by 20 to 90 percent. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis. For management of a suspected drug overdose, contact your regional Poison Control Centre

5. Pharmacological properties

5.1 Mechanism of Action

HQTOR (hydroxychloroquine sulfate tablets) belongs to the 4-aminoquinoline class. HQTOR has been beneficial for patients with rheumatoid arthritis and lupus erythematosus, especially chronic discoid lupus. The exact mode of action in controlling these diseases is unknown. The action of this compound against malarial parasites is similar to that of chloroquine phosphate.

5.2 Pharmacodynamic properties

Mechanism of action

Antimalarial agents like chloroquine and hydroxychloroquine have several pharmacological actions which may be involved in their therapeutic effect in the treatment of rheumatic disease, but the role of each is not known. These include interaction with sulphydryl groups, interference with enzyme activity (including phospholipase, NADH-cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

5.3 Pharmacokinetic properties

Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine. Following oral administration, hydroxychloroquine is rapidly and almost completely absorbed. In one study, mean peak plasma hydroxychloroquine concentrations following a single dose of 400 mg in healthy subjects ranged from 53 –

208 ng/ml with a mean of 105 ng/ml. The mean time to peak plasma concentration was 1.83 hours. The mean plasma elimination half-life varied, depending on the post administration period, as follows: 5.9 hours at C_{max} – 10 hours), 26.1 hours (at 10 – 48 hours and 299 hours (at 48 – 504 hours). The parent compound and metabolites are widely distributed in the body and elimination is mainly via the urine, where 3% of the administered dose was recovered over 24 hours in one study.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Only reported limited preclinical data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the two products.

Genotoxicity

There are limited data on hydroxychloroquine genotoxicity. Chloroquine is reported in the literature to elicit both gene mutations and chromosomal/DNA breaks in some *in vitro* systems but not in others and in *in vivo* studies using rodents when dosed via the intraperitoneal route. Chromosomal effects were not observed *in vivo* when chloroquine was administered orally.

Carcinogenicity

There are no data on hydroxychloroquine carcinogenicity.

In a limited 2-years study in rats with chloroquine, no increase in neoplastic or proliferative changes was observed.

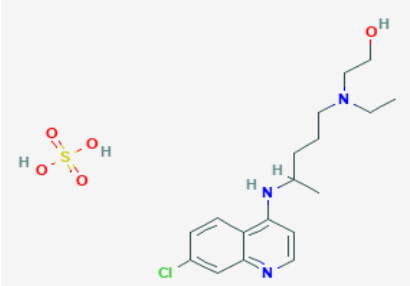
Developmental and reproductive toxicity

There are limited data on hydroxychloroquine teratogenicity. Chloroquine is teratogenic in rats after administration at very high, supratherapeutic doses, i.e. between 250 – 1500 mg/kg/day, showing a fetal mortality rate of 25% and ocular malformations (anophthalmia and microophthalmia) in 45% of foetuses in the 1000 mg/kg/day group. Auto-radiographic studies have shown that when administered at the start or the end of gestation, chloroquine accumulates in the eyes and ears of fetuses.

A study in male rats after 30 days of oral treatment at 5 mg/day of chloroquine showed a decrease in fertility rate, and in testosterone levels, weight of testes, epididymis, seminal vesicles and prostate.

7. Description

Hydroxychloroquine Sulphate is (RS)-2-N-[4-{7-chloro-4-quinolyamino)pentyl]-N-ethylaminoethanol sulphate having molecular weight of 434g/mol and molecular formula of $C_{18}H_{26}ClN_3O,H_2SO_4$. The chemical structure is as below:



Hydroxychloroquine Sulphate is a white or almost white, crystalline powder which is freely soluble in water; practically insoluble in ethanol (95%) and in ether.

HQTOR 200

White colored, round shaped, biconvex film coated tablets plain on both sides. The excipients used are Maize Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Purified Talc, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol, Triacetin, Tribasic Calcium Phosphate and Titanium Dioxide.

HQTOR 400

White colored, round shaped, biconvex film coated tablets plain on both sides. The excipients used are Maize Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Purified Talc, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol, Triacetin, Tribasic Calcium Phosphate and Titanium Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

HQTOR is available in blister strip of 10 tablets.

8.4 Storage and handing instructions.

Store protected from light and moisture, at a temperature not exceeding 30°C.

Keep out of the reach of children.

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What HQTOR is and what it is used for

9.2.What you need to know before you take HQTOR

9.3.How to take HQTOR

9.4.Possible side effects

9.5.How to store HQTOR

9.6.Contents of the pack and other information

9.1.What HQTOR is and what it is used for

HQTOR contains Hydroxychloroquine sulfate works by reducing inflammation in people with autoimmune diseases (this is where the body's immune system attacks itself by mistake).

It can be used for below conditions:

200mg

It is indicated for treatment of acute or chronic rheumatoid arthritis in adult patients and for the treatment of systemic lupus erythematosus.

400mg

It is indicated for treatment of acute or chronic rheumatoid arthritis in adult patients and for the treatment of systemic lupus erythematosus.

As an adjunct to diet and exercise to improve glycemic control of patients on metformin, sulfonylurea combination in patients with Type II Diabetes.

9.2.What you need to know before you take HQTOR

Do not use HQTOR if:

You are allergic to

- hydroxychloroquine sulfate
- any of the other ingredients of HQTOR
- any similar drugs such as chloroquine
- You have retinopathy. This is an eye problem affecting the retina at the back of your eye. HQTOR may cause irreversible damage to your retina. You should tell your doctor right away if you have any **Visual Problems**.
- You are a child below 6 years of age **or** weigh less than 35 kg.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HQTOR. Talk about any health conditions or problems you may have, including if you:

- were born with, now have, or have a family history of long QT interval. HQTOR may cause Heart Rhythm Disorders in some patients. These Heart Rhythm Disorders can be seen on an ECG, or an electrical recording of the heart.

Caution should be taken when taking HQTOR if you:

- have heart disease, which can include heart failure, slow heartbeat, heart palpitations or irregular heartbeat. The risk of heart problems may increase with higher doses of HQTOR.
- have had a heart attack (myocardial infarction)
- have a family history of sudden death from heart attack before the age of 50
- take other drugs that can cause prolonged QT interval

- have a low level of potassium, calcium or magnesium in your blood, or have a condition that may affect the levels of those salts in the blood. Examples are an eating disorder or prolonged vomiting.
- are allergic or sensitive to a drug called to quinine.
- are pregnant, or you are planning to get pregnant. HQTOR may be passed to your unborn baby. HQTOR may harm your unborn baby. Your doctor will evaluate the benefit and risk of using HQTOR during pregnancy.
- Are breastfeeding. HQTOR passes into breast milk in small amounts. Infants can be very sensitive to the toxic effects of drugs like HQTOR. There is not enough HQTOR in breast milk to protect an infant against malaria. The infant should receive their own malaria treatment if necessary. Talk to your doctor about the risks HQTOR can have on your baby. These risks depend on:
    - why you are taking HQTOR;
    - How long you will be taking HQTOR for.
- Have diabetes or symptoms of low blood sugar. HQTOR can cause low blood sugar, and sometimes, low blood sugar can be very dangerous. You may pass out or need to go to the hospital.
- Have liver or kidney disease.
- Have alcoholism.
- Have a blood disease, including a rare blood disease called porphyria. HQTOR can make this worse.
- Have nervous system disease.
- Have a skin disease called psoriasis.
- Have a genetic red blood cell disease known as "glucose-6-phosphate dehydrogenase deficiency".
- Have gastrointestinal disorders. These are problems in the intestines, stomach, or gut.
- Have decreased vision.
- Have weakness in your muscles.
- Have thoughts of suicide or depression.
- Are over 65 years old.

Other warnings you should know about:

HQTOR can cause **long QT interval** or **torsade de pointes**. This is a dangerously fast heart rate. It can lead to cardiac arrest, sudden collapse and death.

Heart problems or failure, cardiomyopathy, an enlarged or weak heart can occur if you take HQTOR for long periods of time. These are serious and can result in death. Your doctor will check your heart regularly.

When you go outside, protect your skin from the sun by:

- wearing appropriate clothing, and

- using sunscreen cream with a minimum SPF 30 rating.

It is unclear whether HQTOR may affect male fertility. Talk to your doctor if you would like to father a child in the future.

Driving and Using Machines: You may have blurry vision when taking HQTOR. Do not drive or do things that require you to be alert. Wait until you know how you respond to HQTOR and can see well. If you continue to have difficulty, your doctor may reduce your dose.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HQTOR:

- Drugs for depression (tricyclic antidepressants) and psychiatric disorders (Antipsychotics).
- Digoxin. If you are taking both HQTOR and digoxin, your doctor may decide to check the level of digoxin in your blood, as the dose may need to be reduced.
- Anti-diabetic drugs, including insulin. If you take HQTOR and a drug for diabetes or high blood sugar, there is a risk of having very low blood sugar. This can be life-threatening. Your doctor may decide to reduce the doses of the drug or insulin to control diabetes.
- Antiepileptic drugs.
- Some antibiotics used for infections (e.g. aminoglycoside antibiotics, erythromycin).
- Neostigmine and pyridostigmine (medicines used to treat muscle disorders).
- Cimetidine (medicine used to treat heartburn).
- Cyclosporine (an immunosuppressant medication).
- Drugs known as CYP2C8 and CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir).
- Medicines that are known to cause cardiac arrhythmias (irregular heartbeats).
- Antacids. You should take antacids at least 4 hours before or 4 hours after taking HQTOR.
- Rabies vaccine.
- Medicines that may affect the liver, the kidney, the skin or the eye.
- Medicines that may increase the risk of convulsions (e.g. antimalarials (mefloquine)).
- Medicines that decrease blood salt levels (e.g. water pills, laxatives, amphotericin B, high dose corticosteroids, and proton pump inhibitors).
- Agalsidase (a medicine used to treat a rare genetic disease called Fabry disease).
- Medicines that may increase risk of retinal toxicity. An example is tamoxifen, which is used to treat breast cancer. When taken alone, both HQTOR and tamoxifen can cause damage to your retina at in the eye. Taking both drugs at the same time can increase your risk of retinal damage.
- Praziquantel (a medicine used to treat some infestations).

9.3.How to take HQTOR

Take HQTOR exactly as your doctor told you to. Never take more HQTOR than your doctor has prescribed.

To help avoid an upset stomach, take HQTOR with a meal or a glass of milk.

Usual dose:

Your doctor will decide on the best dose for you. It may be based on your weight, physical health and other factors such as what other medications you are taking. The dose may need to be stopped or temporarily reduced due to side effects. The dose may then be re-started or increased to an optimum level by your doctor. Your dose will likely be lowered during treatment, after your Initial Dose. You may take the lower dose for a lengthy amount of time. This is called a Maintenance Dose.

Maintenance Dose. **Condition**	**Recommended dose**	**Number of tablets a day**
Rheumatoid Arthritis	Initial: 400 – 600 mg a day	2 - 3
	Maintenance: 200 – 400 mg a day	1 - 2
Lupus Erythematosus	Initial: 400 mg, once or twice a day	2 - 4
	Maintenance: 200 – 400 mg a day	1 - 2
Diabetes	As directed by physician	

Should you have a serious change of health at any point while taking HQTOR, see your doctor.

For patients with RA, SLE or DLE, if HQTOR makes your symptoms completely better, talk to your doctor. They may want to bring down your daily dose. Never change your dose without talking with your doctor first.

Overdose: If you think you have taken too much HQTOR, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Taking too much HQTOR is dangerous and can lead to death. You could have symptoms of overdose within 30 minutes after taking it.

Taking too much HQTOR is also dangerous for children. Children have died by taking too much HQTOR. If you think an infant or small child has swallowed even one pill, immediately take them to the nearest hospital emergency room.

Symptoms of overdose include:

- Headache

- feeling drowsy

- Vision problems, like seeing blurry or in double

- Heart problems like uneven heartbeats or rapid heartbeats

- fainting

- Muscle weakness

- Convulsions

- Serious trouble breathing

Missed Dose:

If you forget to take a dose, take it as soon as you remember. But if it's within twelve hours of your next dose, skip the one you missed and take only the regularly scheduled dose. **Never take a double dose.**

9.4.Possible side effects

These are not all the possible side affects you may feel when taking HQTOR. If you experience any side effects not listed here, contact your healthcare professional.

Before and during your treatment with HQTOR your doctor may do some tests. These may include:

- Blood tests

- An electrocardiogram (ECG)

- A periodic exam of your muscles and tendon reflexes

- complete eye exams

HQTOR can cause permanent **eye damage**. To help prevent this, you should have an eye exam before you start taking HQTOR. You will need more eye exams while you are taking HQTOR.

Side effects

Diarrhea , Vomiting

Anorexia: loss or lack of appetite

Visual problems and damage to the retina of the eye: blurred vision, seeing halos around lights, especially at night. Seeing light flashes and streaks. Night blindness with difficulty seeing at night or in poor light. Visual field loss including blind spots or blind areas in your vision. Change in eye colour. Difficulty focusing your eyes, or skipping words when reading.

Rash, itchy rash with raised red bumps

Nervousness, quick changes in mood (emotional lability)

Change in colour of skin, mucous membranes and hair: bleaching of hair. Loss or increase in skin pigment (bluish-black colour).

Alopecia: hair loss from your head or any part of your body.

Hearing problems: ringing in the ears. Hearing loss.

Nerve and muscle problems: tingling, numbness, burning pain, weakness, cramps, spasms, restlessness, rigidity, tremors, twitches, difficulty walking

Increased sensitivity to sunlight. Skin rash due to sunlight can be reduced by appropriate use of sunscreen creams.

Muscle weakness

Permanent damage to vision

Fainting spells or loss of consciousness

Liver problems: unusual tiredness, nausea, vomiting, abdominal pain, jaundice (yellow discoloration of the eyes or skin), dark urine

Bone Marrow Depression or a decrease in production of cells:

Low White Blood cells (leukocytes): Fever and chills. Infections.

Anemia or low red blood cells (erythrocytes): Fatigue, extreme tiredness that doesn't get better with rest. Paleness of skin, lips, and nail beds.

Low platelets used for blood clotting (thrombocytes): Bleeding: nose bleeds, gums, or mouth. Tiny red spots on the skin

Psychosis: hallucinations, loss of contact with reality

Hypoglycemia or low blood sugar: hunger pains, sweating, shakiness, weakness, dizziness, fast heartbeat, nausea, irritability, blurred vision, confusion, loss of consciousness

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5.How to store HQTOR

Store protected from light and moisture, at a temperature not exceeding 30°C.

9.6.Contents of the pack and other information.

HQTOR 200

Each film coated tablet contains:

Hydroxychloroquine Sulphate I.P 200 mg

The excipients used are Maize Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Purified Talc, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol, Triacetin, Tribasic Calcium Phosphate and Titanium Dioxide.

HQTOR 400

Each film coated tablet contains:

Hydroxychloroquine Sulphate I.P. 400 mg

The excipients used are Maize Starch, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Povidone, Purified Talc, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate Polyvinyl Alcohol, Polyethylene Glycol, Triacetin, Tribasic Calcium Phosphate and Titanium Dioxide.

10. Details of manufacturer

Manufactured by:

Ravenbhel Biotech

EPIP, SIDCO, Kartholi, Bari-Brahmana,

Jammu - 181133

11. Details of permission or licence number with date

Mfg Licence No.: JK/01/11-12/192 issued on 29.07.2015

12. Date of revision

March /2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/HQTOR – 200, 400mg /March -20/01 /PI