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

8032900-9093

HQTOR

(Hydroxychloroquine Sulphate Tablets I.P.)

WARNING

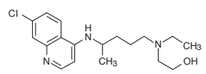
PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING HYDROXYCHLOROQUINE SULPHATE TABLETS.

DESCRIPTION:

Hydroxychloroquine sulphate is a white or practically white, crystalline powder, freely soluble in water, practically insoluble in alcohol, in chloroform and in ether. Chemically, the drug is (±)-2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl] ethylamino]ethanol sulphate (1:1) (salt). The Molecular formula is $C_{18}H_{26}ClN_3O \cdot H_2SO_4$ and the molecular weight: 433.95.

Hydroxychloroquine sulphate tablets contain 200mg hydroxychloroquine sulphate, equivalent to 155 mg base, and are for oral administration.

The structural formula of Hydroxychloroquin is as follows:



Hydroxychloroquine Sulphate $C_{18}H_{26}ClN_3O \cdot H_2SO_4$

COMPOSITION

Each film coated tablet contains :

Hydroxychloroquine Sulphate I.P.	200 mg
Excipients	q.s.

Colour : Titanium Dioxide I.P.

PHARMACOLOGY

Hydroxychloroquine has been found to be useful as an anti-inflammatory, and anti-thrombotic agent. It also produces beneficial effects in conditions associated with light sensitivity. The cellular and molecular mechanisms involved in all these recognised pharmacological actions of hydroxychloroquine are largely unknown.

Hydroxychloroquine is thought to act as a mild immunosupressant, inhibiting the production of rheumatoid factor and acute phase reactants. In rheumatoid arthritis, hydroxychloroquine acts as a DMARD (disease modifying antirheumatic agent). It has several pharmacological actions, which may be involved in their therapeutic effect in the treatment of rheumatoid 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, collagenase, 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. Hydroxy chloroquine therapy may lead to the regression of the skin lesions of discoid or systemic lupus erythematosus. Hydroxychloroquine is thought to have useful photoprotective properties by suppressing abnormal responses to ultraviolet light in sunlight.

PHARMACOKINETICS

Hydroxychloroquine is rapidly and almost completely absorbed orally. Bioavailability is approximately 74%. It is widely distributed in body tissues and concentrates in the spleen, kidneys, liver, melanin containing tissues, lungs to a lesser extent, the spinal cord and brain. Concentrations are 2-5 times higher in erythrocytes than in plasma. Very low concentration is seen in intestinal wall. The drug crosses placenta also. It has moderate protein binding (approximately 45%). It is metabolized in liver, to active de-ethylated metabolites. Hydroxychloroquine has a terminal elimination half-life of approximately 50 days in blood and approximately 32 days in plasma. 23-25% of hydroxychloroquine excreted in urine in unchanged form. Hydroxychloroquine is excreted very slowly; may persist in urine for months or years after medication is discontinued. It is also excreted in bile. Hemodialysis does not remove appreciable amount of hydroxychloroquine from blood.

INDICATIONS

Hydroxychloroquine is indicated for:

1. Acute or chronic rheumatoid arthritis in adult patients
2. Systemic lupus erythematosus
3. Polymorphous light eruption (Under the prescriptions of dermatologist only)

CONTRAINDICATIONS

Hydroxychloroquine is contraindicated:

i. In patients who are hypersensitive to 4-aminoquinoline compounds
ii. In patients with retinal or visual field changes attributable to any 4-aminoquinoline compound
iii. For long term therapy in children
iv. Pre-existing maculopathy of the eye
v. Pregnancy

WARNINGS

General

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. Retinopathy has been reported to be dose related. Ophthalmic examinations, including slit-lamp, funduscopic, and visual field tests, should be performed prior to initiation to hydroxychloroquine therapy and annually (as per the American College of Rheumatology (ACR) guidelines, 2002) during therapy whenever long-term use of the drug is contemplated.

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

Patient should be advised to stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted. The occurrence of retinopathy is very uncommon if the recommended daily dose is not exceeded. The administration of doses in excess of the recommended maximum is likely to increase the risk of retinopathy, and accelerates its onset.

This ophthalmic examination should be done more frequently in the following situations:

- Daily dosage exceeds 6.5 mg/kg lean body weight
- Renal insufficiency
- Visual acuity below 6/8
- Age above 65 years.
- Cumulative dose more than 200 g

Hydroxychloroquine should be used with caution in patients taking medicines, which may cause adverse ocular or skin reactions.

Caution should also be applied when it is used in patients with hepatic or renal disease, in those taking drugs known to affect those organs, and in patients with severe gastrointestinal, neurological or blood disorders. Estimation of plasma hydroxychloroquine level should be under taken in patients with severely compromised renal or hepatic function and dosage adjusted accordingly.

Use of hydroxychloroquine in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria, the condition may be exacerbated. Hydroxychloroquine should not be used in these conditions unless in the judgment of physician the benefit to the patient outweighs the possible hazard.

Although the risk of bone marrow depression is low, periodic blood counts are advisable as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells, and thrombocytopenia have been reported and hydroxychloroquine should be discontinued if abnormalities develop. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Patients receiving prolonged therapy with hydroxychloroquine should be questioned and examined periodically for the evidence of muscular weakness; knee and ankle reflexes should be tested. If muscular weakness occurs during therapy with hydroxy-chloroquine, the drug should be discontinued.

PRECAUTIONS

Because hydroxychloroquine may concentrate in liver, the drug should be used with caution in patients with hepatic disease or alcoholism and in conjunction with known hepatotoxic drugs. Periodic blood cell counts should be made if patients are given prolonged therapy. Hydroxychloroquine should be discontinued if there is evidence of adverse hematologic effects that are severe and not attributable to the disease being treated. The drug should be administered with caution to patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.

Dermatologic reactions to hydroxychloroquine may occur and therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis. If serious toxic symptoms occur, administer ammonium chloride (8g daily in divided doses for adults) 3 or 4 days a week for several months after therapy has been stopped; acidification of the urine increases renal excretion by 20% to 90%. Exercise caution in metabolic acidosis.

Effects on ability to drive and use machines :

Hydroxychloroquine may cause dizziness. Impaired visual accommodation soon after the treatment has been reported and patients should be warned regarding driving or operating machinery. If the condition is not self-limiting, it will resolve on reducing the dose or stopping treatment.

Usage in pregnancy and lactation

Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. It should be noted that 4-amino quinolines 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. Therefore hydroxychloroquine should not be used in pregnancy.

Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Usage in paediatrics

The minimum effective dose should be employed and should not exceed 6.5mg/kg/day based on ideal body weight. The 200mg and 400mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg. Small children are particularly sensitive to the toxic effects of 4-amino quinolines; therefore patients should be warned to keep the drug out of the reach of children.

Front Side
144 mm

Usage in geriatrics

No special precautions are necessary in elderly patients provided that renal function is normal.

Drug interactions

Hydroxychloroquine sulphate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in-patients receiving combined therapy.

Hydroxychloroquine sulphate may also be subjective to several known interactions, which include: potentiation of its direct blocking at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of hydroxychloroquine; antagonism effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human-diploid cell rabies vaccine.

Antacids may reduce absorption hydroxychloroquine so it is advised that a 4 hour interval be observed between hydroxychloroquine and antacid dosing. Concurrent use of penicillamine with hydroxychloroquine may increase penicillamine plasma concentrations, increasing the potential for serious hematologic and/or renal adverse reactions, as well as the possibility of severe skin reactions.

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

ADVERSE DRUG REACTIONS

The lower toxicity of hydroxychloroqine makes it more popular for use in conditions where relatively high drug dosages are required over long periods.

Ocular side effects

Ciliary body: Disturbance of accommodation with symptoms of blurred vision. This reaction is dose-related and reversible with cessation of therapy.

Retina: Retinopathy with changes in pigmentation and visual field defects can occur, but appears to be uncommon, if the recommended daily dose is not exceeded. In its early form it appears reversible on discontinuation of hydroxy chloroquine. If allowed to develop, 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 and abnormal colour vision.

Cornea: Corneal changes including oedema and opacities, transient opacities have been reported. They are symptomless or may cause disturbances such as halos, blurring vision or photophobia. Corneal deposits may appear as early as 3 weeks following initiation of therapy. They may be transient and are reversible on stopping treatment.

Other fundus changes include optic disc pallor and atrophy, attenuation of retinal arterioles, fine granular pigmentary disturbances in the peripheral retina and prominent choroidal patterns in advanced stage.

Dermatological side effects

Skin rashes some times occur; pigmentary changes in skin and mucous membrane, bleaching of hair and hair losses have also been reported. These usually resolve readily on stopping treatment. Bullous eruptions including very rare cases of erythema multiforme and Stevens-Johnson syndrome, photosensitivity and isolated cases of exfoliative dermatitis have been reported. Very rare cases of acute generalised exanthematous pustulosis (AGEP) has to be distinguished from psoriasis, although hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favourable after drug withdrawal.

Gastrointestinal side effects

These include nausea, diarrhea, anorexia, abdominal cramps and rarely, vomiting. These symptoms usually resolve immediately on reducing the dose or stopping treatment.

CNS side effects

Irritability, nervousness, emotional changes, nightmares, toxic psychosis, hearing loss, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia have been reported with this class of drugs.

Neuromuscular side effects

Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction. Myopathy may be reversible after drug discontinuation, but recovery may take many months.

Hematologic side effects

Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydro genase deficiency). Rarely, there have been reports of bone-marrow depression.

Cardiovascular side effects

Cardiomyopathy has been rarely reported with high daily dosages of hydroxy chloroquine. Chronic toxicity should be suspected when conduction disorders (bundle branch block/atrioventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

Liver side effects

Isolated cases of abnormal liver function tests have been reported; rare cases of fulminant hepatic failure have also been reported.

Allergic reactions

Urticaria, angioedema and bronchospasm have been reported.

Miscellaneous

Weight loss, lassitude, exacerbation or precipitation of porphyria and nonlight-sensitive psoriasis. Hypoglycemia is rare but well recognized adverse effect of hydroxychloroquine.

DOSAGE AND ADMINISTRATION

Rheumatoid arthritis: The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, where as minor side effects may occur relatively 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 discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial dosage- In adults, from 400 mg to 600 mg (= 310mg to 465 mg base) daily in divided doses, each dose to be taken with a meal or a glass of milk. In a small percentage of patients, troublesome side effects may require temporary reduction of the initial dosage. Later (usually from five to ten days) the dose may gradually be increased to the optimal response level, often without return of side effects.

Maintenance dosage - When a good response is obtained (usually in 4 to 12 weeks), the dosage is reduced by 50% and continued at a usual maintenance level of 200mg to 400mg (= 155 mg to 310 mg base) daily, each dose to be taken with a meal or a glass of milk. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

If relapse occur after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Corticosteroids and salicylates may be used in conjunction with compound, and they can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. The tablets are for oral administration. Each dose should be taken with a meal or glass of milk.

Lupus erythematosus: Initially the average adult dose is 400 mg (= 310 mg base) 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 mg to 400 mg (=155 to 310 mg base) daily will frequently suffice.The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Polymorphous light eruption: 400mg daily in the first month and then 200mg daily for 2-3 months depending on the clinical response.

Renal impairment :

In renal impairment, the dose of hydyroxychloroquine sulphate for long term follows:

use needs to be reduced according to the glomerular filtration rate (GFR) as

GFR 20-50 ml min-1	Maximum 75 mg daily
GFR 10-20 ml min-1	Maximum 50 mg daily
GFR less than 10ml min-1	Contraindicated

OVERDOSAGE

Overdosage with the 4-aminoquinolines is especially dangerous in infants. About 1-2g has proved fatal. Death can occur within 2h of overdosage. An adult male is reported to have survived an overdose of 36 tablets (200 mg per tablet) and a plasma level of 6.1mg/L.The symptoms of massive overdose may include headache, visual disturbances, cardiovascular collapse and convulsions, hypokalaemia, and rhythm and conduction disorders followed by sudden and early respiratory and cardiac arrest. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest. Since these effects may appear soon after taking a massive dose, treatment should be prompt and symptomatic. The stomach should be immediately evacuated either by emesis or by gastric lavage. Finely powdered charcoal in a dose at least five times of the overdose may inhibit further absorption if introduced into the stomach by tube following lavage and within 30 minutes of ingestion of the overdose. 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, it should be corrected by oxygen administration, artificial respiration or, in shock with hypotension, by vasopressor therapy. Exchange transfusions have been used to reduce the level of 4-aminoquinoline drug in the blood.

Consideration should be given to administration of parenteral diazepam in cases of overdosage. It has been shown to be beneficial in reversing chloroquine cardiotoxicity. Respiratory support may be needed and the need for intubation or tracheostomy considered. Shock should be treated by the administration of fluid (with plasma expanders if necessary) with central venous pressure monitoring. In severe cases, the administration of dopamine should be considered. A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 hours.

EXPIRY DATE:

Do not use later than expiry date.

STORAGE

Store below 30^{0}C, protected from light & moisture. Keep out of reach of children.

PRESENTATION

Hqtor is available as 200 mg in blister strip of 10 tablets.

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Registered Office :
Ipca Laboratories Ltd.
48, Kandivli Ind. Estate, Mumbai - 400 067.

IFDJR1

Back Side
144 mm