W =180 mm, H = 267 mm

UNIQUIN

(Hydroxychloroquine Sulfate 200mg Film Coated Tablet)

Name and Strength of active Ingredient
Each tablet contains Hydroxychloroquine Sulfate BP 200 mg.

Description
Round shaped, light yellow colored film coated tablet having score line on one side and 'INCEPTA' debossed on other.

Pharmacodynamics
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 polymorph nuclear cell chemotax is and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

Pharmacokinetics
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 400mg in healthy subjects ranged from 53-208ng/ml with a mean of 105ng/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 Cmax-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.

Indication
Treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

Recommended Dosage
Adults (including the elderly)
The minimum effective dose should be employed. This dose should not exceed 6.5mg/kg/day (calculated from ideal body weight and not actual body weight) and will be either 200mg or 400mg per day.

In patients able to receive 400mg daily
Initially 400mg daily in divided doses. The dose can be reduced to 200mg when no further improvement is evident. The maintenance dose should be increased to 400mg daily if the response lessens.

Paediatric population
The minimum effective dose should be employed and should not exceed 6.5mg/kg/day based on ideal body weight. The 200mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg. Each dose should be taken with a meal or glass of milk. Hydroxychloroquine is cumulative in action and will require several weeks to exert its beneficial effects, whereas minor side effects may occur relatively early. For rheumatic disease treatment should be discontinued if there is no improvement by 6 months. In light-sensitive diseases, treatment should only be given during periods of maximum exposure to light.

Route of Administration
Oral

Contraindications
- Hypersensitivity to hydroxychloroquine or to any of the excipients known hypersensitivity to 4-aminoquinoline compounds
- Pre-existing maculopathy of the eye
- Pregnancy (see Pregnancy and lactation)

Warning and Precautions
General • 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 accelerate its onset. • All patients should have an ophthalmological examination before initiating treatment with Hydroxychloroquine sulfate. Thereafter, ophthalmological examinations must be repeated at least every 12 months. The examination should include testing visual acuity, careful ophthalmoscopy, fundoscopy, central visual field testing with a red target, and colour vision. This examination should be more frequent and adapted to the patient in the following situations: - daily dosage exceeds 6.5mg/kg lean body weight. Absolute body weight used as a guide to dosage could result in an overdosage in the obese. - renal insufficiency - visual acuity below 6/8 - age above 65 years - cumulative dose more than 200 g. Hydroxychloroquine sulfate should be discontinued immediately in any patient who develops a pigmentary abnormality, visual field defect, or any other abnormality not explainable by difficulty in accommodation or presence of corneal opacities. Patients should continue to be observed for possible progression of the changes. Patients should be advised to stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted, including abnormal colour vision.

Hydroxychloroquine sulfate 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 the following:
- Patients with hepatic or renal disease, and in those taking drugs known to affect those organs. Estimation of plasma hydroxychloro quine levels should be undertaken in patients with severely compro mised renal or hepatic function and dosage adjusted accordingly.
- Patients with severe gastrointestinal, neurological or blood disorders. 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. Hydroxychloroquine sulfate should be discontinued if abnormalities develop. Caution is also advised in patients with a sensitivity to quinine, those with glucose- -phosphate dehydro genase deficiency, and those with porphyria cutanea tarda which can be exacerbated by hydroxychloroquine and in patients with psoriasis since it appears to increase the risk of skin reactions.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Small children are particularly sensitive to the toxic effects of 4-amino quinolines; therefore patients should be warned to keep Hydroxychloroquine sulfate out of the reach of children.
- All patients on long-term therapy should undergo periodic examination of skeletal muscle function and tendon reflexes. If weakness occurs, the drug should be withdrawn.
- Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications.
- Patients treated with hydroxychloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms.
- Patients presenting with clinical symptoms suggestive of hypogly caemia during treatment with hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Suicidal behaviour and psychiatric disorders • Suicidal behaviour and psychiatric disorders have been reported in some patients treated with hydroxychloroquine. Psychiatric side effects typically occur within the first month after the start of treatment with hydroxychloroquine and have been reported also in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

Drug Induced Phospholipidosis
Cases of hydroxychloroquine induced phospholipidosis have been reported during use of Uniquin (see section Adverse Effects). Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle. Monitoring for toxicity is advised.
Discontinue Uniquin if cardiac, renal, or muscle toxicity related to drug induced phospholipidosis is suspected or demonstrated by tissue biopsy.

Aggravation of Myasthenia Gravis
Aggravation of symptoms of myasthenia gravis (generalized weakness including shortness of breath, dysphagia, diplopia, ptosis etc.) have been reported in myasthenic patients receiving hydroxychloroquine therapy. Discontinue Uniquin if aggravation of symptoms related to myasthenia gravis is suspected.

Interactions with Other Medicaments
Digoxin
Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

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

Drugs known to prolong the QT interval/with potential to induce cardiac arrthyhmia
Hydroxychloroquine should be used with caution in patients receiving drugs known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia. Halofantrine should not be administered with hydroxychloroquine.
There may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

Ciclosporin
An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered.

Tamoxifen
Concomitant use of drugs known to induce retinal toxicity, e.g. tamoxifen and hydroxychloroquine sulfate, is not recommended.

Agalsidase
There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

Drugs affecting the convulsive threshold
Hydroxychloroquine can lower the convulsive threshold.

Co-administration of hydroxychloroquine with other anti-malarials known to lower the convulsion threshold (e.g mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine.

Hydroxychloroquine sulfate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include:

- potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics
- inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial
- antagonism of effect of neostigmine and pyridostigmine
- reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between hydroxychloroquine sulfate and antacid dosing.

In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-admin istered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine. There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase

Effects on ability to Drive or Operate Machinery
Impaired visual accommodation soon after the start of the treatment had 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.

Pregnancy and Lactation
Pregnancy: Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. It should be noted that 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. Therefore UNIQUIN should not be used in pregnancy.
Data from a population-based cohort study including 2045 hydroxychloroquine exposed pregnancies suggests a small increase in the relative risk (RR) of congenital malformations associated with hydroxychloroquine exposure in the first trimester (n = 112 events). For a daily dose of ≥ 400 mg the RR was 1.33 (95% CI, 1.08 – 1.65). For a daily dose of < 400 mg the RR was 0.95 (95% CI, 0.60 – 1.50).

Lactation: Careful consideration should be given to using hydroxy chloroquine 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.

Side Effects
Ocular effects: 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 UNIQUIN. 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. Corneal changes including oedema and opacities have been reported. They are either symptomless or may cause disturbances such as haloes, blurring of vision or photophobia. They may be transient and are reversible on stopping treatment. Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible may also occur.

Dermatologic effects: Skin rashes sometimes occur; pruritus, pigmentary changes in skin and mucous membranes, bleaching of hair and alopecia 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 effects: Gastrointestinal disturbances such as nausea, diarrhoea, anorexia, abdominal pain and, rarely, vomiting may occur. These symptoms usually resolve immediately on reducing the dose or on stopping treatment.

CNS effects: Less frequently, dizziness, vertigo, tinnitus, hearing loss, headache, nervousness, emotional lability, toxic psychosis and convulsions have been reported with this class of drugs.

Neuromuscular effects: Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups have been noted.
Myopathy may be reversible after drug discontinuation, but recovery may take many months. Associated mild sensory changes, depression of tendon reflexes and abnormal nerve conduction may be observed.

Cardio-vascular effects: Cardiomyopathy has been rarely reported. 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.

Hematologic effects: Rarely, there have been reports of bone-marrow depression. Blood disorders such as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells and thrombocytopenia have been reported. Hydroxychloroquine may precipitate or exacerbate porphyria.

Liver 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.

Metabolism and nutrition disorders: Hypoglycaemia. Frequency: unknown.
Frequency 'not known': phospholipidosis*
*Cases of hydroxychloroquine induced phospholipidosis have been reported. Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle causing toxicity (see section Warnings and Precautions).

SOC Psychiatric disorders:
Common: Affect lability
Uncommon: Nervousness
Not known: suicidal behaviour, psychosis, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.

Skin and subcutaneous tissue disorders:
Frequency 'not known': Sweet's syndrome

Symptoms and Treatment of Overdose
Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2g having proved fatal. The symptoms of over dosage may include headache, visual disturbances, cardiovascular collapse, convulsions, hypokalaemia, and rhythm and conduction disorders, followed by sudden and early respiratory and cardiac 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. Activated 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. Consideration should be given to administration of parenteral diazepam in cases of over dosage; it has been shown to be beneficial in reversing chloroquine cardiotoxicity. Respiratory support and shock management should be instituted as necessary.

Storage Conditions
Store below 30 °C. Keep away from light.

Shelf Life
36 months

Packaging
6 x 10's tablets are packed in 250µm clear PVC/ 20µm aluminum foil blister packed in an outer carton along with package insert.

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