1.3 Product Information

1.3.2 Package Leaflet

Package leaflet is presented in subsequent pages**.**

PRESCRIBING INFORMATION: For the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

HYDROXYCHLOROQUINE SULFATE TABLETS USP 200 mg

RHUMATAS

Composition
Each film coated tablet contains:
Hydroxychloroquine Sulfate USP 200 mg
equivalent to 155 mg of hydroxychloroquine
Colour: Titanium Dioxide
Excipients: Q.S.

THERAPEUTIC INDICATIONS

Adults

Hydroxychloroquine Sulfate tablets are recommended for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

This product is also indicated in adults for prevention and treatment of uncomplicated malaria caused by *Plasmodium vivax*, *P. ovale*, *P.malariae* and chloroquine sensitive *P. falciparum*.

Paediatric Population

Treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.
Also indicated for prevention and treatment of uncomplicated malaria, caused by *Plasmodium vivax*, *P. malariae*, *P. ovale* and chloroquine-sensitive *P. falciparum*.

POSOLOGY AND METHOD OF ADMINISTRATION

Hydroxychloroquine Sulfate tablets are for oral administration. 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.

Rheumatoid Arthritis
Adults (including the elderly)
Initial dose: 400 mg per day
With a good response, the daily dose can be reduced after three months.
Maintenance dose: 200 mg per day

Paediatric Population
The minimum effective dose should be employed and should not exceed 6.5 mg/kg/day based on ideal body weight. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg.

Systemic and Discoid Lupus Erythematodes
Adults: initial dose 400 mg to 600 mg per day (several weeks if necessary).
Maintenance dose: 200 mg to 400 mg per day.

Polymorphic photodermatoses
adults: 400 mg per day is usually enough

Malaria
Prophylaxis of malaria
Adults: 400 mg per week on the same day of each week.
Children: The minimum effective dose should be employed and should not exceed 6.5 mg/kg/day based on ideal body weight. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg.
Prophylaxis should start and continue one week before arrival in an area with malaria be up to four or eight weeks after departure from that area.

Treatment of an acute attack of malaria
Adults: initial dose of 800 mg followed by 6-8 hours by 400 mg and then 400 mg on each of the next two days (total 2 grams of hydroxychloroquine sulfate).
For the treatment of an attack of a *Plasmodium falciparum* infection and an acute attack of *Plasmodium vivax* infection is to suppress a single dose of 800 mg is sufficient.
When prescribing a treatment, official guidelines and local information about it occurrence of resistance to anti-malarial drugs should be considered. Examples of this include WHO and public health guidelines.
Treatment of infection with *Plasmodium malariae* , *vivax* and *oval* should be completed with treatment with an 8-aminoquinoline for the extra-erythrocytic phase of the plasmodium cycle to eliminate.
Children: 10 mg / kg in children is comparable to 800 mg in adults and 5 mg / kg in children is comparable to 400 mg in adults.
A total dosage of up to 2 grams is administered over three days, as follows:
- First dose: 10 mg per kg (maximum once-only 800 mg).
- Second dose: 5 mg per kg (maximum 400 mg) 6 hours after the first dose.
- Third dose: 5 mg per kg (maximum 400 mg) 18 hours after the second dose.
- Fourth dose: 5 mg per kg (maximum 400 mg) 24 hours after the third dose

Reduced kidney and liver function
Caution should be exercised in patients with impaired renal or hepatic function. A reduction in dosage may be required.

CONTRAINDICATIONS

- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye
- pregnancy
- below 6 years of age (200 mg tablets not adapted for weight <31 kg)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

- All patients should have an ophthalmological examination before treatment with Hydroxychloroquine Sulfate tablets is initiated. Thereafter, ophthalmological examinations must be repeated at least every 12 months.
- Retinal toxicity is largely dose-related. The risk of retinal damage is small with daily doses of up to 6.5 mg/kg body weight. Exceeding the recommended dose sharply increases the risk of retinal toxicity.

The examination should include testing visual acuity and colour vision, careful ophthalmoscopy, fundoscopy and central visual field testing with a red target.

This examination should be more frequent and adapted to the patient in the following situations:

- daily dosage exceeds 6.5 mg/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 tablets should be discontinued immediately in any patient who develops a pigmentary abnormality, visual field defect or any other abnormalities not explained by difficulty in accommodation (see also section 4.8). Patients should continue to be observed as retinal changes and visual disturbances may progress even after cessation of therapy.

Concomitant use of hydroxychloroquine with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with Hydroxychloroquine. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Hydroxychloroquine Sulfate tablets should be discontinued if cardiomyopathy develops. Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed.

Hydroxychloroquine Sulfate tablets 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 medicines known to affect those organs. Estimation of plasma hydroxychloroquine levels should be undertaken in patients with severely compromised renal or hepatic function, and dosage adjusted accordingly.
- patients with severe gastrointestinal, neurological or blood disorders.

Caution is also advised in patients with a sensitivity to quinine, those with glucose-6-phosphate dehydrogenase deficiency, 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.

Although the risk of bone-marrow depression is low, periodic blood counts are advisable in all patients on long-term therapy and Hydroxychloroquine Sulfate tablets should be discontinued if abnormalities develop.

Suicidal behaviour has been reported in very rare cases in patients treated with hydroxychloroquine.

Small children are particularly sensitive to the toxic effects of 4-aminoquinolines; therefore, patients should be warned to keep Hydroxychloroquine Sulfate tablets 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.

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

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 hypoglycaemia during treatment with hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Extrapyramidal disorders may occur with Hydroxychloroquine.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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.

Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

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

Administration of hydroxychloroquine with antimalarials known to lower the convulsion threshold (e.g mefloquine) may increase the risk of convulsions.

The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

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

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 coadministered. 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 coadministered with agalsidase.

Concurrent use with drugs with oculotoxic or haemotoxic potential should be avoided if possible.

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

FERTILITY, 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 Hydroxychloroquine should not be used in pregnancy unless considered essential by the physician.

Lactation

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.

UNDESIRABLE EFFECTS

The following 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, thrombocytopenia.

Immune system disorders
Not known: Urticaria, angioedema, bronchospasm

Metabolism and nutrition disorders
Common: Anorexia
Not known: Hypoglycemia
Hydroxychloroquine may exacerbate porphyria.

Psychiatric disorders
Common: Affect lability
Uncommon: Nervousness
Not known: Psychosis, suicidal behaviour

Nervous system disorders
Common: Headache
Uncommon: Dizziness
Not known: Convulsions have been reported with this class of drugs.
Extrapyramidal disorders such as dystonia, dyskinesia, tremor

Eye disorders
Common: Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible
Uncommon: Retinopathy, with changes in pigmentation and visual field defects. In its early form, it appears reversible on discontinuation of hydroxychloroquine. 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 edema and opacities have been reported.

They are either symptomless or may cause disturbances such as halos, blurring of vision, or photophobia. They may be transient or are reversible on stopping treatment.
Not known: Cases of maculopathies and macular degeneration have been reported and may be irreversible.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus
Not known: Hearing loss

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 / atrio-ventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

Gastrointestinal disorders
Very common: Abdominal pain, nausea
Common: Diarrhoea, vomiting
These symptoms usually resolve immediately on reducing the dose or on stopping the treatment.

Hepatobiliary disorders
Uncommon: Abnormal liver function tests
Not known: Fulminant hepatic failure

Skin and subcutaneous tissue disorders
Common: Skin rash, pruritus
Uncommon: Pigmentation disorders in skin and mucous membranes, bleaching of hair, alopecia. These usually resolve readily on stopping treatment.
Not known: Bullous eruptions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), photosensitivity, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP). 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.

Musculoskeletal and connective tissue disorders
Uncommon: Sensorymotor disorders
Not known:
Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Myopathy may be reversible after drug discontinuation, but recovery may take many months. Depression of tendon reflexes and abnormal nerve conduction studies.

OVERDOSE

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

The symptoms of overdosage may include headache, visual disturbances, cardiovascular collapse, convulsions, hypokalaemia, rhythm and conduction disorders, including QT prolongation, torsade de pointe, ventricular tachycardia and ventricular fibrillation, followed by sudden and potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose.

The stomach should be immediately evacuated, either by emesis or by gastric lavage. Activated charcoal in a dose at least five times that of the overdosage 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 overdosage; it has been shown to be beneficial in reversing chloroquine cardiotoxicity.

Respiratory support and shock management should be instituted as necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Anti rheumatic
ATC code: P01BA02

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.

Pharmacokinetic properties

Hydroxychloroquine is rapidly absorbed following oral administration. Mean bioavailability is approximately 74%. It is widely distributed throughout the body, accumulating within blood cells and other tissues such as liver, lungs, kidneys and eyes. It is partially converted to active ethylated metabolites in the liver and eliminated principally via the kidney, 23 to 25% unchanged, but also via the bile. Excretion is slow, the terminal elimination half-life being approximately 50 days (whole blood) and 32 days (plasma).

Hydroxychloroquine crosses the placenta and is likely to resemble chloroquine in entering breast milk.

STORAGE

Store below 30°C.

SHELF LIFE

2 Years

PRESENTATION

Hydroxychloroquine sulfate tablets are available in Clear PVC-Alu Blister of 10 Tablets.

Manufactured by:
INTAS
INTAS PHARMACEUTICALS LTD.
Matoda-382 210, Dist.: Ahmedabad. INDIA