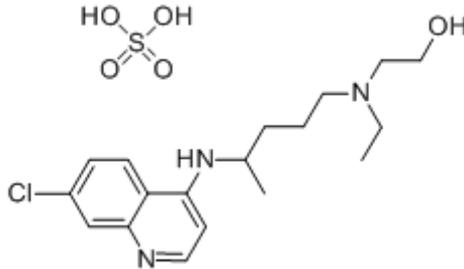


APO- HYDROXYCHLOROQUINE TABLETS**NAME OF THE MEDICINE**

Hydroxychloroquine sulfate.

Chemical Name: (RS)-2-N-[4-(7-chloro-4-quinolylamino)pentyl]-N-ethylaminoethanol sulfate

Structural Formula:



Molecular Formula: $C_{18}H_{26}ClN_3O \cdot H_2SO_4$

Molecular Weight: 433.95

CAS Registry Number: 747-36-4

DESCRIPTION

Hydroxychloroquine sulfate is a colourless crystalline solid, soluble in water to at least 20%.

Each tablets contains 200mg of Hydroxychloroquine sulphate as the active ingredient.

In addition, each tablet contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, starch - pregelatinised maize, hypromellose, magnesium stearate, polysorbate 80, silica colloidal anhydrous and Opadry II White 85F18422.

PHARMACOLOGY**Pharmacological Actions**

Hydroxychloroquine is an anti-malarial. It also exerts a beneficial effect in mild systemic and discoid lupus erythematosus and rheumatoid arthritis. The precise mechanism of action is not known.

Like chloroquine phosphate, hydroxychloroquine is highly active against the erythrocytic forms of *Plasmodium vivax* and *P. malariae* and most strains of *P. falciparum* (but not the gametocytes of *P. falciparum*).

Hydroxychloroquine does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria, it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum*.

INDICATIONS

Rheumatoid arthritis; mild systemic and discoid lupus erythematosus; the suppression and treatment of malaria.

CONTRAINDICATIONS

Hydroxychloroquine is contraindicated in:

- patients with pre-existing maculopathy of the eye;
- patients with known hypersensitivity to 4-aminoquinoline compounds;
- long-term therapy in children;
- children under 6 years of age.

PRECAUTIONS

Hydroxychloroquine is not effective against chloroquine-resistant strains of *P. falciparum*.

Patients should be warned to keep hydroxychloroquine out of the reach of children, as small children are particularly sensitive to 4-aminoquinolines.

Hydroxychloroquine should be used with caution, or not at all, in patients with severe gastrointestinal, neurological or blood disorders. If such severe disorders occur during therapy, hydroxychloroquine should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Hydroxychloroquine should not be used in these conditions unless in the judgement of the physician, the benefit to the patient outweighs the possible risk.

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 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 has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without anti-diabetic 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.

Ophthalmological Reactions

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinolone therapy for discoid and systemic lupus erythematosus or rheumatoid arthritis. Retinopathy has been reported to be dose related.

If there is any indication of abnormality in the visual field or retinal macular areas (such as pigmentary changes, 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, hydroxychloroquine should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy.

All patients being treated with hydroxychloroquine should have an initial ophthalmological examination. Ophthalmological testing should be conducted at 6-monthly intervals in patients receiving hydroxychloroquine at a dose of not more than 6 mg/kg body weight per day.

Ophthalmological testing should be conducted at 3–4 monthly intervals in the following circumstances:

- dose exceeds 6 mg/kg ideal (lean) body weight per day. Using absolute body weight, as a guide to dosage, could result in an overdosage in the obese;
- significant renal impairment;
- significant hepatic impairment;
- elderly;
- complaints of visual disturbances;
- duration of treatment exceeds 8 years.

The examination should include slit-lamp microscopy (for corneal opacities) and fundus and visual field studies. A complete eye examination before treatment will determine the presence of any visual abnormalities, either coincidental or due to the disease, and establish a baseline for further assessment of the patient's vision.

Corneal changes often subside on reducing the dose or on interrupting therapy for a short period of time, but any suggestion of retinal change or restriction in the visual field is an indication for complete withdrawal of the drug.

The use of sunglasses in patients exposed to strong sunlight is recommended, as this may be an amplifying factor in retinopathy.

Observe caution in patients with hepatic or renal disease, in whom a reduction in dosage may be necessary, as well as in those taking medicines known to affect these organs. Also observe caution in patients with gastrointestinal, neurological, or blood disorders, in those with a sensitivity to quinine and in glucose-6-phosphate dehydrogenase deficiency, porphyria and psoriasis.

Skin Reactions

Pleomorphic skin eruptions (morbilliform, lichenoid, purpuric), itching, dryness and increased pigmentation sometimes appear after a few months of therapy. The rash is usually mild and transient. If a rash appears, hydroxychloroquine should be withdrawn and only started again at a lower dose.

Patients with psoriasis appear to be more susceptible to severe skin reactions than other patients.

Haematological Reactions

Patients on long-term therapy should have periodic full blood counts. If evidence of agranulocytosis, anaemia, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, hydroxychloroquine should be discontinued.

Miscellaneous

Gastrointestinal disturbances such as nausea, anorexia, abdominal cramps or rarely vomiting, occur in some patients. The symptoms usually stop on reducing the dose or temporarily stopping the drug.

Muscle weakness, vertigo, tinnitus, nerve deafness, headache and nervousness have been reported less frequently.

All patients on long-term therapy with hydroxychloroquine should be questioned and examined periodically, including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs discontinue the drug.

In the treatment of rheumatoid arthritis, if objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months, hydroxychloroquine should be discontinued. Safe use of hydroxychloroquine in the treatment of juvenile rheumatoid arthritis has not been established.

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

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

Extrapyramidal disorders may occur with hydroxychloroquine.

Use in Pregnancy (Category D)

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 haemorrhages and abnormal retinal pigmentation.

The use of hydroxychloroquine in the treatment of malaria or suppression of malaria in high risk situations may be justified if the treating physician considers the risk to the foetus is outweighed by the benefits to the mother and foetus.

When used in high doses and for prolonged periods, chloroquine and related substances may cause neurological disturbances and interference with hearing, balance and vision in the foetus.

Use in Lactation

Nursing Mothers: Careful consideration should be given to using hydroxychloroquine during lactation, since it has been known 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-aminoquinones.

INTERACTIONS WITH OTHER MEDICINES

It has been suggested that 4-aminoquinolines are pharmacologically incompatible with monoamine oxidase inhibitors.

Concomitant hydroxychloroquine and digoxin therapy may result in increased serum digoxin concentrations. Consequently, serum digoxin concentrations should be closely monitored in patients receiving concomitant therapy.

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

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.

Increased plasma cyclosporin levels have been reported when cyclosporin and hydroxychloroquine are co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarial 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.

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-administered. 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.

ADVERSE EFFECTS

Note:

- *very common* $\geq 1/10$ ($\geq 10\%$)
- *common* $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)
- *uncommon* $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)
- *rare* $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
- *very rare* $< 1/10,000$ ($< 0.01\%$)
- *not known* frequency cannot be estimated from the available data

Ophthalmological

Common: blurring of vision

Uncommon: corneal changes, retinal changes

Not known: cases of maculopathies and macular degeneration have been reported and may be irreversible.

Corneal changes including oedema and opacities have occurred from three weeks (infrequently) to some years after the beginning of therapy. 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. Should these types of corneal changes occur with hydroxychloroquine, it should be either stopped or temporarily withdrawn.

Reversible extra-ocular muscle palsies and temporary blurring of vision due to interference with accommodation have also been noted.

Retinal changes such as abnormal macular pigmentation and depigmentation (sometimes described as a "bull's eye"), pallor of the optic disc, optic atrophy and narrowing of the retinal arterioles have been reported.

Retinopathy with changes in pigmentation and visual field defects have been rarely reported. 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 even have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour visions. Originally, the condition was thought to be progressive and irreversible, but more recent evidence suggests that routine ophthalmological examinations may detect retinal changes, especially pigmentation, at an early and reversible stage when there is no apparent visual disturbance.

Much evidence suggests that there is a threshold of dosage above which retinopathy appears. These results seem to correlate more with daily dosage than with a cumulative dose, although the risk increases with increased duration of treatment.

It is recommended that all patients have an initial ophthalmological examination, repeated at 6-month intervals during therapy. This should include slit-lamp microscopy, fundus and visual field studies.

Any adverse changes in the ocular findings or the appearance of scotoma, night blindness or other retinal changes require immediate discontinuation of hydroxychloroquine; these patients should not subsequently receive any pharmacologically similar drugs.

Allergic Reactions

Not known: urticaria, angioedema, bronchospasm

Blood Disorders

Rare: bone marrow depression, anaemia, aplastic anaemia, leukopenia, thrombocytopenia.

Very rare: agranulocytosis.

Hydroxychloroquine may exacerbate porphyria.

Central Nervous System Disorders

Common: affect lability, headache

Uncommon: vertigo, tinnitus, nerve deafness, nervousness, dizziness.

Rare: convulsions, neuromyopathy.

Very rare: psychosis, suicidal behaviour, nightmares, nystagmus, ataxia

Not known: hearing loss, extrapyramidal disorders such as dystonia, dyskinesia, tremor.

Neuromuscular

Uncommon: sensory motor disorders

Not known: absent or hypoactive deep tendon reflexes, muscle weakness or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups (muscle weakness may be reversible after drug discontinuation, but recovery may take many months). Depression of the tendon reflex and abnormal nerve conduction may be observed.

Very rare: extraocular muscle palsies.

Gastrointestinal

Very common: abdominal pain, nausea

Common: diarrhoea

Rare: vomiting.

Metabolism and nutrition disorders

Common: anorexia
Not known: hypoglycaemia

Liver Disorders

Uncommon: abnormal liver function tests.
Very rare: fulminant hepatitis.

Cardiovascular Disorders

Rare: cardiomyopathy which may result in cardiac failure, and in some cases a fatal outcome (see PRECAUTIONS)

Dermatological

Common: skin rashes, alopecia, pruritus.
Uncommon: pigmentary changes, bleaching of hair
Very rare: acute generalized exanthematous pustulosis, exfoliative dermatitis and erythema multiforme, Stevens-Johnson syndrome, Drug rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), toxic epidermal necrolysis, photosensitivity.

Miscellaneous

Rare: exacerbation or precipitation of porphyria and attacks of psoriasis.
Very rare: weight loss, lassitude.

DOSAGE AND ADMINISTRATION**Rheumatoid Arthritis**

Hydroxychloroquine is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur relatively early. Several months of therapy may be required before maximum effects can be obtained.

Initial dosage: In adults, a suitable initial dosage is from 400–600 mg daily, preferably taken at meal times. In a few patients the side effects may require temporary reduction of the initial dosage. Generally, after 5–10 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 4–12 weeks) the dose can be reduced to 200–400 mg daily (but should not exceed 6 mg/kg per day) and can be continued as maintenance treatment. The minimum effective maintenance dose should be employed. The incidence of retinopathy has been reported to be higher when the maintenance dose is exceeded.

If objective improvement (such as reduced joint swelling or increased mobility) does not occur within six months the drug should be discontinued.

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

Safe use of hydroxychloroquine for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Hydroxychloroquine 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 hydroxychloroquine has been used for several weeks. When gradual reduction of steroid dosage is suggested, it may be done by reducing every 4–5 days the dose of cortisone by no more than 5–15 mg; of methylprednisolone from 1–2 mg and dexamethasone from 0.25–0.5 mg. Treatment regimens using agents other than corticosteroids and NSAIDs are under development. No definitive dose combinations have been established.

Lupus Erythematosus

In mild systemic and discoid cases, antimalarials are the drugs of choice.

The dose of hydroxychloroquine depends on the severity of the disease and the patient's response to treatment. For adults, an initial dose of 400–800 mg daily is recommended. This level can be maintained for several weeks and then reduced to a maintenance dose of 200–400 mg daily.

Malaria

Hydroxychloroquine is active against the erythrocytic forms of *P. vivax* and *P. malariae* and most strains of *P. falciparum* (but not the gametocytes of *P. falciparum*).

Hydroxychloroquine does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exo-erythrocytic forms, nor will it prevent vivax or malariae infection when administered as a prophylactic.

It is effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum*.

Malaria Suppression

Adults

400 mg (310 mg base) on exactly the same day of each week.

Children

The weekly suppressive dose is 5 mg (base) per kg bodyweight, but should not exceed the adult dose regardless of weight.

Suppressive therapy should begin two weeks prior to exposure. Failing this, in adults an initial loading dose of 800 mg (620 mg base), or in children 10 mg base per kg, may be taken in two divided doses, six hours apart. The suppressive therapy should be continued for eight weeks after leaving the endemic area.

Treatment of the Acute Attack

Adults

An initial dose of 800 mg followed by 400 mg 6–8 hours later and then 400 mg on each of two consecutive days (total dose of 2 g or 1.55 g base). A single dose of 800 mg (620 mg base) has also proved effective.

Children

The dosage is calculated on the basis of bodyweight (total dose of 25 mg base per kg).

- First dose - 10 mg base per kg (not exceeding a single dose of 620 mg base).
- Second dose - 5 mg base per kg (not exceeding 310 mg base), six hours after first dose.
- Third dose - 5 mg base per kg eighteen hours after second dose.
- Fourth dose - 5 mg base per kg twenty-four hours after third dose.

For radical cure of vivax and malariae malaria, concomitant therapy with an 8-aminoquinoline is necessary.

OVERDOSAGE

Symptoms

Overdosage with 4-aminoquinolines is dangerous. Children are particularly sensitive to these compounds and a number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 or 1 gram in one 3 year old child).

The 4-aminoquinolines are very rapidly and completely absorbed after ingestion and toxic symptoms following overdosage may occur within 30 minutes. Toxic symptoms consist of headache, drowsiness, visual disturbances, hypokalaemia cardiovascular collapse and convulsions followed by sudden and early respiratory and cardiac arrest. The ECG may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time including QT prolongation, torsade de pointe, ventricular tachycardia and

progressive bradycardia leading to ventricular fibrillation and/or cardiac arrest. Immediate medical attention is required as these effects may appear shortly after the overdose.

Treatment

Treatment is symptomatic and must be prompt. Emesis is not recommended because of the potential for CNS depression, convulsions and cardiovascular instability. Gastric lavage may be indicated if performed soon after ingestion or in patients who are comatose. In obtunded or comatose patients receiving gastric lavage the airway should be protected. Activated charcoal should be administered. The dose of activated charcoal should be at least five times the estimated amount of hydroxychloroquine ingested.

Consideration should be given to using diazepam parenterally as there have been reports that it may decrease cardiotoxicity.

Respiratory support and management of shock should be instituted as necessary.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

APO-Hydroxychloroquine tablets are intended for oral administration.

Each tablet contains 200 mg hydroxychloroquine sulphate, as the active ingredient.

200mg tablets:

White to off-white, capsule-shaped tablets, debossed "HCQS" on one side, plain on the other side.

Bottles (white round HDPE with white polypropylene child resistance cap with a heat sensitive liner) of 100 tablets (AUST R 186393).

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
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Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

03 April 2012

DATE OF MOST RECENT AMENDMENT

17 October 2016