PRODUCT INFORMATION

PLAQUENIL

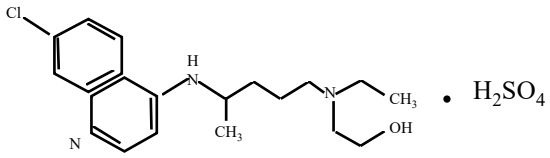
NAME OF MEDICINE

AUSTRALIAN APPROVED NAME

Hydroxychloroquine sulfate

CHEMICAL STRUCTURE

Hydroxychloroquine sulfate is designated chemically as 2 {N (4-(7-Chloro-4-quinolylamino)pentyl)- -N-ethylamino}ethanol sulfate, and has the following chemical structure:



$C_{18}H_{26}ClN_3O$, H_2SO_4 Molecular Weight: 433.96

CAS REGISTRY NUMBER

747-36-4 (hydroxychloroquine sulfate)
118-42-3 (hydroxychloroquine).

DESCRIPTION

Film coated tablets containing hydroxychloroquine sulfate 200 mg (equivalent to 155 mg base). The tablets also contain the inactive ingredients calcium hydrogen phosphate, maize starch, purified water, and magnesium stearate. The film coating contains small amounts of hypromellose, macrogol 400, titanium dioxide, polysorbate 80, carnauba wax, black ink (Tekprint SB-9014SD), and purified water.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

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

Malaria

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

Plaquenil 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

Plaquenil is contraindicated in:

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

PRECAUTIONS

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

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

Plaquenil 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, the drug should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Plaquenil 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 Plaquenil. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Plaquenil 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

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, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy. (See adverse reactions section)

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 per kg body weight per day.

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

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used 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 patents 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, Plaquenil 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, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, Plaquenil 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 this preparation 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, the drug should be discontinued. Safe use of the drug 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 this drug 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.

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 anitmalarials 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*	≥ 1/10 (≥ 10%)
	common	≥ 1/100 and < 1/10 (≥ 1% and <10%)
	uncommon	≥1/1000 and < 1/100 (≥ 0.1% and <1.0%)
	rare	≥1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	very rare	< 1/10,000 (< 0.01%)
	not known	frequency cannot be estimated from 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 Plaquenil, 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 Plaquenil. 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 six-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 Plaquenil; 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, leucopenia, thrombocytopenia

Very rare: agranulocytosis

Hydroxychloroquine may exacerbate porphyria

Central Nervous System

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 tendon reflexes and abnormal nerve conduction studies

Very rare: extraocular muscle palsies

Gastrointestinal

Very common: abdominal pain, nausea

Common: diarrhoea, 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 generalised exanthematous pustolosis (AGEP), 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

Plaquenil 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 to 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 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 dose can be reduced to 200 to 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 Plaquenil for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Plaquenil 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 methylprednisolone from 1 to 2 mg and dexamethasone from 0.25 to 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, the antimalarials are the drugs of choice.

The dosage of Plaquenil 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

Plaquenil 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).

Plaquenil 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 in six to eight hours and 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 the 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.

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

White to off-white peanut shaped tablets, marked "Plaquenil" in black ink on one face of the tablet. Plaquenil is supplied as 100 tablets in an HDPE bottle.

Plaquenil tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

19 August 1994

DATE OF MOST RECENT AMENDMENT

18 September 2015

Plaquenil Tablets

hydroxychloroquine sulfate

Consumer Medicine Information (CMI)

Please read this leaflet before you start to take this medicine.

What is in this leaflet

This leaflet answers some common questions about Plaquenil Tablets. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. In deciding to give you Plaquenil, your doctor has weighed the risks of taking Plaquenil against the benefits it will have for you.

Keep this information with the tablets. You may wish to read it again later.

What is Plaquenil used for

Plaquenil may be used for any of the following conditions:

Rheumatoid arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterised by stiffness, swelling and pain. Plaquenil may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, Plaquenil may slow down the process of joint damage and relieve the symptoms of the disease.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterised by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterised by chills, fever and sweats.

In malaria, Plaquenil destroys the harmful parasite which causes the illness.

Your doctor may have prescribed this medicine for another reason. Ask your doctor if you have any questions about why Plaquenil has been prescribed for you.

Plaquenil is not addictive. This medicine is available only with a doctor's prescription.

Before you take Plaquenil

When you must not take Plaquenil

Do not take Plaquenil if you have ever had an allergic reaction to hydroxychloroquine, chloroquine, or related products or any of the ingredients listed under "Product Description".

If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

The symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.

Ask your doctor about the risks and benefits of taking Plaquenil while you are pregnant.

When Plaquenil is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

Ask your doctor about the risks and benefits of taking Plaquenil while you are breastfeeding.

Do not take Plaquenil if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.

Plaquenil should not be used in children under 6 years.

Plaquenil should not be used in children over 6 years for long periods.

Do not take Plaquenil after the expiry date printed on the bottle.

It may have no effect at all, or worse, an entirely unexpected effect if you take it after the expiry date.

Do not take Plaquenil if the bottle is damaged or shows signs of tampering.

Do not take Plaquenil to treat any other complaint unless your doctor says it is safe. Do not give this medicine to anyone else.

Before you start to take Plaquenil

You must tell your doctor if:

- You are allergic to quinine.
- You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
- You have any pre-existing eye disorders.
- You have experienced low blood sugar levels (hypoglycaemia - a "hypo"). Plaquenil may increase the risk of you having a hypo.
- You have or have had any of these medical conditions:

- Chloroquine-resistant malaria
- Liver or kidney problems
- Diabetes
- Stomach, brain or blood disorders
- Disease of the heart muscle
- Skin diseases, in particular psoriasis which is a kind of itchy rash.
- Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
- Porphyria, which is a rare disease of blood pigments.

If you have not told your doctor about any of these things, tell him/her before you take any Plaquenil.

Taking Plaquenil with other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines may interfere with Plaquenil. These include:

- Any medicine to treat depression
- Digoxin - a medicine used to treat heart disease
- Medicines to treat diabetes
- Medicines used to suppress the immune system such as cyclosporin
- Antiarrythmic drugs such as amiodarone
- Other antimalarial drugs
- Medicines to treat epilepsy

These medicines may be affected by Plaquenil or affect the way Plaquenil works.

Your doctor or pharmacist can tell you what to do if you are taking any of these medicines.

How to take Plaquenil

Swallow tablets whole with a little water or other liquid.

It is best to take Plaquenil at meal times.

The dosage will depend on why you are being treated with Plaquenil.

The usual doses are:

Rheumatoid arthritis

Adults

2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE

Adults

2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria Symptoms

Adults

2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of malaria

Adults

The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for you.

Plaquenil should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your pharmacist or doctor.

If you forget to take Plaquenil

If you are being given Plaquenil for rheumatoid arthritis, SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given Plaquenil for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much Plaquenil (Overdose)

Immediately telephone your doctor, or the Poisons Information Centre (in Australia telephone 13 11 26 and in New Zealand telephone 0800 POISON or 0800 764766), or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Plaquenil.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too many tablets you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While you are taking Plaquenil

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking Plaquenil.

Tell all doctors, dentists and pharmacists who are treating you that you are taking Plaquenil.

Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers.

These symptoms may be associated with hypoglycaemia.

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets
- unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognise the symptoms of hypoglycaemia and know how to treat them.

Your doctor will need to perform the following tests during treatment with Plaquenil:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, Plaquenil has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Tests

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Your doctor may monitor your blood sugar levels if you have experienced hypoglycaemia while taking Plaquenil.

Driving/Operating Machinery

Be careful driving or operating machinery until you know how Plaquenil affects you.

Plaquenil may cause problems with the eyesight of some people. Make sure you know how you react to Plaquenil before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while taking Plaquenil.

Plaquenil helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions.

Tell your doctor if you notice any of the following and they worry you:

Less serious side effects

Stomach problems such as:

- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:

- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking Plaquenil.

More serious side effects

Tell your doctor if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Suicidal behaviour

- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:

- disorientation
- seizures, fits or convulsions
- loss of consciousness

These are serious side effects. You may need urgent medical attention.

Serious side effects are rare.

Tell your doctor if you notice anything else that is making you feel unwell.

Some people may get other side effects while taking Plaquenil.

After taking Plaquenil

Storage

Keep your tablets in the bottle until it is time to take them.

If you take the tablets out of the bottle they will not keep well.

Keep it in a cool dry place where the temperature stays below 25°C.

Heat and dampness can destroy some medicines. Do not leave Plaquenil in the car on hot days.

Do not store Plaquenil or any other medicine in the bathroom or near a sink.

Keep Plaquenil where young children cannot reach it.

Children are particularly sensitive to the unwanted effects of Plaquenil.

A locked cupboard at least one and a half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking the tablets, ask your pharmacist what to do with any tablets that are left over.

Product Description

What Plaquenil looks like

Plaquenil comes as white to off-white peanut shaped tablets marked "PLAQUENIL" with black ink. A bottle contains 100 tablets.

Ingredients

Active Ingredient

Each Plaquenil tablet contains 200mg hydroxychloroquine sulfate.

Other ingredients

- Calcium Hydrogen Phosphate
- Starch-Maize
- Magnesium Stearate
- Water-Purified
- hypromellose
- Macrogol 400
- Titanium dioxide
- Polysorbate 80
- Carnauba Wax
- Black Ink

Australian Registration Number

AUST R 50055

Supplier

Plaquenil is supplied in Australia by:

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park NSW 2113

Plaquenil is supplied in New Zealand by:

sanofi-aventis new zealand limited

56 Cawley St

Ellerslie, Auckland, New Zealand

Phone: (09) 580 1810

This leaflet was prepared in April 2014.

plaquenil-ccdsv8-cmiv6-02apr14

PRODUCT INFORMATION

PLAQUENIL

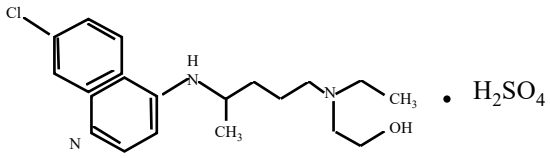
NAME OF MEDICINE

AUSTRALIAN APPROVED NAME

Hydroxychloroquine sulfate

CHEMICAL STRUCTURE

Hydroxychloroquine sulfate is designated chemically as 2 {N (4-(7-Chloro-4-quinolylamino)pentyl)- -N-ethylamino}ethanol sulfate, and has the following chemical structure:



$C_{18}H_{26}ClN_3O$, H_2SO_4 Molecular Weight: 433.96

CAS REGISTRY NUMBER

747-36-4 (hydroxychloroquine sulfate)
118-42-3 (hydroxychloroquine).

DESCRIPTION

Film coated tablets containing hydroxychloroquine sulfate 200 mg (equivalent to 155 mg base). The tablets also contain the inactive ingredients calcium hydrogen phosphate dihydrate, maize starch, purified water, and magnesium stearate. The film coating contains small amounts of hypromellose, macrogol 400, titanium dioxide, polysorbate 80, carnauba wax, black ink (Tekprint SB-9014SD,), and purified water.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

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

Malaria

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

Plaquenil 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

Plaquenil is contraindicated in:

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

PRECAUTIONS

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

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

Plaquenil 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, the drug should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Plaquenil 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 Plaquenil. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Plaquenil 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

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. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity.

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, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy. (See adverse reactions section)

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

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 per kg body weight per day.

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

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used 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 patents 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, Plaquenil 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, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, Plaquenil 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 this preparation 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, the drug should be discontinued. Safe use of the drug 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. Hydroxychloroquine should be avoided in pregnancy except when, in the judgement of the physician, the potential benefits outweigh the potential hazards.

The use of this drug 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.

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 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.

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*	≥ 1/10 (≥ 10%)
	common	≥ 1/100 and < 1/10 (≥ 1% and <10%)
	uncommon	≥1/1000 and < 1/100 (≥ 0.1% and <1.0%)
	rare	≥1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	very rare	< 1/10,000 (< 0.01%)
	not known	frequency cannot be estimated from 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 Plaquenil, 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 Plaquenil. 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 six-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 Plaquenil; 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, leucopenia, thrombocytopenia

Very rare: agranulocytosis

Hydroxychloroquine may exacerbate porphyria

Central Nervous System

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 tendon reflexes and abnormal nerve conduction studies

Very rare: extraocular muscle palsies

Gastrointestinal

Very common: abdominal pain, nausea

Common: diarrhoea, 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)

Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed.

Dermatological

Common: skin rashes, alopecia, pruritus

Uncommon: pigmentary changes, bleaching of hair

Very rare: acute generalised exanthematous pustolosis (AGEP), 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

Plaquenil 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 to 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 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 dose can be reduced to 200 to 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 Plaquenil for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Plaquenil 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 methylprednisolone from 1 to 2 mg and dexamethasone from 0.25 to 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, the antimalarials are the drugs of choice.

The dosage of Plaquenil 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

Plaquenil 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).

Plaquenil 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 in six to eight hours and 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 the 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.

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

White to off-white peanut shaped tablets, marked "Plaquenil" in black ink on one face of the tablet. Plaquenil is supplied as 100 tablets in an HDPE bottle.

Plaquenil tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

19 August 1994

DATE OF MOST RECENT AMENDMENT

20 February 2017

Plaquenil Tablets

hydroxychloroquine sulfate

Consumer Medicine Information (CMI)

Please read this leaflet before you start to take this medicine.

What is in this leaflet

This leaflet answers some common questions about Plaquenil Tablets. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. In deciding to give you Plaquenil, your doctor has weighed the risks of taking Plaquenil against the benefits it will have for you.

Keep this information with the tablets. You may wish to read it again later.

What is Plaquenil used for

Plaquenil may be used for any of the following conditions:

Rheumatoid arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterised by stiffness, swelling and pain. Plaquenil may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, Plaquenil may slow down the process of joint damage and relieve the symptoms of the disease.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterised by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterised by chills, fever and sweats.

In malaria, Plaquenil destroys the harmful parasite which causes the illness.

Your doctor may have prescribed this medicine for another reason. Ask your doctor if you have any questions about why Plaquenil has been prescribed for you.

Plaquenil is not addictive. This medicine is available only with a doctor's prescription.

Before you take Plaquenil

When you must not take Plaquenil

Do not take Plaquenil if you have ever had an allergic reaction to hydroxychloroquine, chloroquine, or related products or any of the ingredients listed under "Product Description".

If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

The symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.

Ask your doctor about the risks and benefits of taking Plaquenil while you are pregnant.

When Plaquenil is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

Ask your doctor about the risks and benefits of taking Plaquenil while you are breastfeeding.

Do not take Plaquenil if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.

Plaquenil should not be used in children under 6 years.

Plaquenil should not be used in children over 6 years for long periods.

Do not take Plaquenil after the expiry date printed on the bottle.

It may have no effect at all, or worse, an entirely unexpected effect if you take it after the expiry date.

Do not take Plaquenil if the bottle is damaged or shows signs of tampering.

Do not take Plaquenil to treat any other complaint unless your doctor says it is safe. Do not give this medicine to anyone else.

Before you start to take Plaquenil

You must tell your doctor if:

- You are allergic to quinine.
- You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
- You have any pre-existing eye disorders.
- You have experienced low blood sugar levels (hypoglycaemia - a "hypo"). Plaquenil may increase the risk of you having a hypo.
- You have or have had any of these medical conditions:

- Chloroquine-resistant malaria
- Liver or kidney problems
- Diabetes
- Stomach, brain or blood disorders
- Disease of the heart muscle
- Skin diseases, in particular psoriasis which is a kind of itchy rash.
- Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
- Porphyria, which is a rare disease of blood pigments.

If you have not told your doctor about any of these things, tell him/her before you take any Plaquenil.

Taking Plaquenil with other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines may interfere with Plaquenil. These include:

- Any medicine to treat depression
- Digoxin - a medicine used to treat heart disease
- Medicines to treat diabetes
- Medicines used to suppress the immune system such as cyclosporin
- Antiarrythmic drugs such as amiodarone and moxifloxacin
- Other antimalarial drugs
- Medicines to treat epilepsy
- Tamoxifen (a medicine used to treat breast cancer)

These medicines may be affected by Plaquenil or affect the way Plaquenil works.

Your doctor or pharmacist can tell you what to do if you are taking any of these medicines.

How to take Plaquenil

Swallow tablets whole with a little water or other liquid.

It is best to take Plaquenil at meal times.

The dosage will depend on why you are being treated with Plaquenil.

The usual doses are:

Rheumatoid arthritis

Adults

2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE

Adults

2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria Symptoms

Adults

2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of malaria

Adults

The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for you.

Plaquenil should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your pharmacist or doctor.

If you forget to take Plaquenil

If you are being given Plaquenil for rheumatoid arthritis, SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given Plaquenil for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much Plaquenil (Overdose)

Immediately telephone your doctor, or the Poisons Information Centre (in Australia telephone 13 11 26 and in New Zealand telephone 0800 POISON or 0800 764766), or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Plaquenil.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too many tablets you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While you are taking Plaquenil

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking Plaquenil.

Tell all doctors, dentists and pharmacists who are treating you that you are taking Plaquenil.

Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers.

These symptoms may be associated with hypoglycaemia.

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets
- unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognise the symptoms of hypoglycaemia and know how to treat them.

Your doctor will need to perform the following tests during treatment with Plaquenil:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, Plaquenil has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Tests

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Your doctor may monitor your blood sugar levels if you have experienced hypoglycaemia while taking Plaquenil.

Driving/Operating Machinery

Be careful driving or operating machinery until you know how Plaquenil affects you.

Plaquenil may cause problems with the eyesight of some people. Make sure you know how you react to Plaquenil before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while taking Plaquenil.

Plaquenil helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions.

Tell your doctor if you notice any of the following and they worry you:

Less serious side effects

Stomach problems such as:

- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:

- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking Plaquenil.

More serious side effects

Tell your doctor if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Suicidal behaviour

- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:

- disorientation
- seizures, fits or convulsions
- loss of consciousness

These are serious side effects. You may need urgent medical attention.

Serious side effects are rare.

Tell your doctor if you notice anything else that is making you feel unwell.

Some people may get other side effects while taking Plaquenil.

After taking Plaquenil

Storage

Keep your tablets in the bottle until it is time to take them.

If you take the tablets out of the bottle they will not keep well.

Keep it in a cool dry place where the temperature stays below 25°C.

Heat and dampness can destroy some medicines. Do not leave Plaquenil in the car on hot days.

Do not store Plaquenil or any other medicine in the bathroom or near a sink.

Keep Plaquenil where young children cannot reach it.

Children are particularly sensitive to the unwanted effects of Plaquenil.

A locked cupboard at least one and a half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking the tablets, ask your pharmacist what to do with any tablets that are left over.

Product Description

What Plaquenil looks like

Plaquenil comes as white to off-white peanut shaped tablets marked "PLAQUENIL" with black ink. A bottle contains 100 tablets.

Ingredients

Active Ingredient

Each Plaquenil tablet contains 200mg hydroxychloroquine sulfate.

Other ingredients

- Calcium Hydrogen Phosphate Dihydrate
- Starch-Maize
- Magnesium Stearate
- Water-Purified
- hypromellose
- Macrogol 400
- Titanium dioxide
- Polysorbate 80
- Carnauba Wax
- Black Ink

Australian Registration Number

AUST R 50055

Supplier

Plaquenil is supplied in Australia by:

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park NSW 2113

Plaquenil is supplied in New Zealand by:

sanofi-aventis new zealand limited

56 Cawley St

Ellerslie, Auckland, New Zealand

Phone: (09) 580 1810

This leaflet was prepared in February 2017.

plaquenil-ccdsv10-cmiv7-feb17

PRODUCT INFORMATION

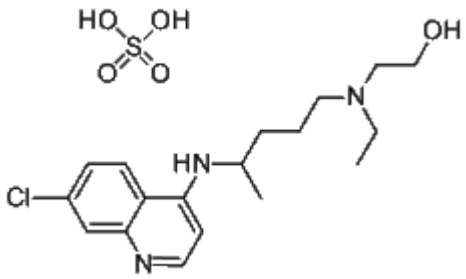
HEQUINEL TABLETS 200 MG

NAME OF THE MEDICINE

Hydroxychloroquine sulfate

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

Structural Formula:



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

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 tablet contains 200 mg hydroxychloroquine sulfate, which is equivalent to 155 mg base. In addition, each tablet contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, pregelatinised maize starch, hypromellose, magnesium stearate, polysorbate 80, colloidal anhydrous silica and Proprietary Ingredient Opadry II White 85F18422.

PHARMACOLOGY

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.

Malaria

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

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. (See adverse reactions section)

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.

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 this drug 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.

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 combination 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 level has been reported when cyclosporin and hydroxychloroquine are co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other anitmalarials 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
- *very rare* < 1/10,000 (< 0.01%)
- *not known* frequency cannot be estimated from 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 can occur but is rare. 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 Disorders

Not known: urticaria, angioedema, bronchospasm

Blood Disorders

Rare: bone marrow depression, anaemia, aplastic anaemia, leukopenia, thrombocytopenia.
Very rare: agranulocytosis.
Hydroxychloroquine may exacerbate porphyria.

Cardiovascular Disorders

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

Central Nervous System Disorders

Common: affect lability, headache
Uncommon: vertigo, tinnitus, headache, nerve deafness, nervousness, dizziness.
Rare: convulsions, neuromyopathy.
Very rare: psychosis, suicidal behaviour, nightmares, nystagmus, ataxia
Not known: hearing loss

Dermatological

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

Gastrointestinal

Very common: abdominal pain, nausea
Common: diarrhoea, vomiting,

Metabolism and nutrition disorders

Common: anorexia
Not known: hypoglycaemia

Liver Disorders

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

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 tendon reflexes and abnormal nerve conduction studies
Very rare: extraocular muscle palsies.

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

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.

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.

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 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 parentally 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 over dosage.

PRESENTATION AND STORAGE CONDITIONS

200 mg tablets

White to off-white, capsule-shaped tablets, embossed “HCQS” on one side, plain on the other side.

Packaged in HDPE bottles of 100 tablets.

Hequinel tablets 200 mg are intended for oral administration.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharma Pty Ltd
34-36 Chandos Street
St-Leonards NSW 2065

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

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

02 February 2015

DATE OF MOST RECENT AMENDMENT

29 April 2015

Hequinel Tablets 200 mg

hydroxychloroquine sulfate 200 mg film coated tablets

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about hydroxychloroquine. It does not contain all the available information.

It does not take the place to talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you using hydroxychloroquine against the benefits they expect it will have for you.

If you have any concerns about using this medicine, 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.

Read this leaflet carefully before you start using this medicine because it contains important information for you.

Keep this leaflet.

You may need to read it again.

What HEQUINEL is used for

The name of your medicine is Hequinel Tablets 200 mg. It contains the active ingredient hydroxychloroquine sulfate.

It may be used for any of the following conditions:

Rheumatoid Arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain.

Hydroxychloroquine may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, hydroxychloroquine may slow down the process of joint damage and relieve the symptoms of the disease.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterized by chills, fever and sweats. In malaria, hydroxychloroquine destroys the harmful parasite which causes the illness.

Your doctor may have prescribed hydroxychloroquine for another reason.

Ask your doctor if you have any questions about why this medicine has been prescribed for you. Hydroxychloroquine is not addictive. This medicine is available only with a doctor's prescription.

Before you use HEQUINEL

When you must not use it

Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet.

If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

Symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.

Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.

Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.

Hydroxychloroquine should not be used in children under 6 years.

Hydroxychloroquine should not be used in children over 6 years for long periods.

Do not take this medicine after the expiry date (EXP) printed on the pack.

It may have no effect at all, or worse, an entirely unexpected effect if you take it after the expiry date.

Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.

Do not take this medicine to treat any other complaint unless your doctor says it is safe.

Do not give this medicine to anyone else.

Before you start to use HEQUINEL

You must tell your doctor if:

1. You are allergic to quinine.
2. You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
3. You have any pre-existing eye disorders
4. You have experienced low blood sugar levels (hypoglycaemia – a "hypo"). Hydroxychloroquine may increase the risk of you having a hypo.
5. You have or have had any of these medical conditions:
   - Chloroquine-resistant malaria
   - Liver or kidney problems
   - Diabetes
   - Stomach, brain or blood disorders
   - Disease of the heart muscle
   - Skin diseases, in particular psoriasis which is a kind of itchy rash
   - Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
   - Porphyria, which is a rare disease of blood pigments.
6. You plan to become pregnant or breast-feed.

If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines
Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and hydroxychloroquine may interfere with each other. These include:

- Any medicine to treat depression
- Digoxin - a medicine used to treat heart disease
- Medicines to treat diabetes
- Medicines used to suppress the immune system such as cyclosporine
- Antiarrythmic drugs such as amiodarone
- Other antimalarial drugs
- Medicines to treat epilepsy

These medicines may be affected by hydroxychloroquine or may affect how well it works.

Your doctor and pharmacist can tell you if you are taking any of these medicines.

How To Take HEQUINEL

Follow all directions given to you by your doctor or pharmacist carefully.

Swallow tablets whole with a little water or other liquid. It is best to take it at meal times.

How much to take

Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.

The dosage will depend on why you are being treated with hydroxychloroquine.

The usual doses are:

Rheumatoid arthritis
Adults
2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE
Adults
2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria
Symptoms
Adults
2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria
Adults
The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.
Your doctor will work out the correct dose for you.

Hydroxychloroquine should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your pharmacist or doctor.

How long to take it for

Continue taking your medicine for as long as your doctor tells you. Make sure you have enough to last over weekends and holidays.

If you forget to take it

If you are being given hydroxychloroquine for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given hydroxychloroquine for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 for Australia) for advice, or go to the Accident and Emergency Department at the nearest hospital, if you think that you or anyone else may have taken too much hydroxychloroquine.

Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

If you take too much hydroxychloroquine, you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While You Are Taking HEQUINEL

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking hydroxychloroquine.

Tell all doctors, dentists and pharmacists who are treating you that you are taking hydroxychloroquine.

Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers. These symptoms may be associated with hypoglycaemia. If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets
- unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognize the symptoms of hypoglycaemia and know how to treat them. Your doctor will need to perform the following tests during treatment with hydroxychloroquine:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, hydroxychloroquine has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Tests

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Your doctor may monitor your blood sugar levels if you have experienced hypoglycaemia while taking hydroxychloroquine.

Driving/Operating Machinery

Be careful driving or operating machinery until you know how Hydroxychloroquine affects you. Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Things you must do

Tell any other doctors, dentists, and pharmacists who are treating you that you are taking Hydroxychloroquine.

Tell your doctor immediately if you become pregnant.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

Go to your doctor regularly for a check-up.

Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.

Things you must not do

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.

Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of

Be careful while driving or operating machinery until you know how hydroxychloroquine affects you.

Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects of HEQUINEL

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking hydroxychloroquine.

Hydroxychloroquine helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor or pharmacist if you notice any of the following and they worry you:

Less serious side effects

- Stomach problems such as:
- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps
- Other problems such as:
- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking hydroxychloroquine.

More serious side effects

Tell your doctor if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Suicidal behavior

- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:
  - disorientation
  - seizures, fits or convulsions
  - loss of consciousness

These are serious side effects. You may need medical attention.

Serious side effects are rare. Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell

Some people may get other side effects while taking hydroxychloroquine.

After Using HEQUINEL

Storage

Keep your medicine in its original packaging until it is time to take it.

If you take your medicine out of its original packaging it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 25°C.

Heat and dampness can destroy some medicines. Do not leave hydroxychloroquine in the car on hot days.

Do not store your medicine, or any other medicine, in the bathroom or near a sink.

Do not leave it on a window sill or in the car.

Heat, sunlight and dampness can destroy some medicines.

Keep it where children cannot reach it.

Children are particularly sensitive to the unwanted effects of hydroxychloroquine.

A locked cupboard at least one and a-half metre above the ground is a good place to store medicines.

Disposal

If your doctor or pharmacist tells you to stop taking this medicine or it has passed its expiry date, ask your pharmacist what to do with any medicine that is left over.

Where to go for further information

Pharmaceutical companies are not in a position to give people an individual diagnosis or medical advice. Your doctor or pharmacist is the best person to give you advice on the treatment of your condition.

Product Description

What Hequinel Tablets looks like?

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

Packaged in bottles of 100 tablets.

Ingredients
Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient (equivalent to 155 mg hydroxychloroquine).

It also contains the following inactive ingredients:
- anhydrous calcium hydrogen phosphate
- pregelatinised maize starch
- hypromellose
- magnesium stearate
- polysorbate 80
- colloidal anhydrous silica
- Opadry II White 85F18422.

This medicine is gluten-free, lactose free and free of other azo dyes.

Sponsor

Aspen Pharma Pty Ltd
34-36 Chandos Street
St-Leonards
NSW 2065

This leaflet was last updated in April 2015.

Australian Registration Number:
AUST R 223696

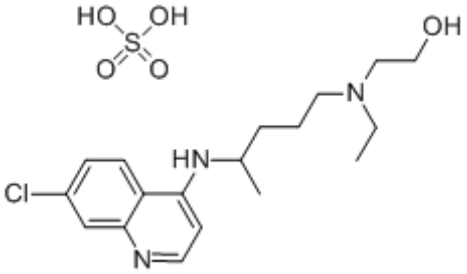
APO- HYDROXYCHLOROQUINE TABLETS

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 patents 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 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 pustolosis, 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 overdosage.

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
16 Giffnock Avenue
Macquarie Park NSW 2113

APO and APOTEX are registered trademarks of Apotex Inc.

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

APO-Hydroxychloroquine

Contains the active ingredient, hydroxychloroquine sulfate

Consumer Medicine Information

For a copy of a large print leaflet, Ph: 1800 195 055

What is in this leaflet

Read this leaflet carefully before taking your medicine. Ask your doctor or pharmacist if you do not understand anything or are worried about taking your medicine.

This leaflet answers some common questions about hydroxychloroquine.

It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the last page. Some more recent information on your medicine may be available. Speak to your pharmacist or doctor to obtain the most up-to-date information.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

Pharmaceutical companies cannot give you medical advice or an individual diagnosis.

Keep this leaflet with your medicine. You may want to read it again.

What this medicine is used for

The name of your medicine is APO-Hydroxychloroquine. It contains the active ingredient hydroxychloroquine sulfate.

It may be used for any of the following conditions:

Rheumatoid Arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain. Hydroxychloroquine may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, hydroxychloroquine may slow down the substances which harm the joints.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterized by chills, fever and sweats.

In malaria, hydroxychloroquine destroys the harmful parasite which causes the illness.

Your doctor may have prescribed hydroxychloroquine for another reason.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

This medicine is available only with a doctor's prescription.

Hydroxychloroquine is not addictive.

Before you take this medicine

When you must not take it

- **Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet.**

  If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

  Symptoms of an allergic reaction may include an asthma attack,

facial swelling, skin rash or hay fever.

- **Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.**

  When hydroxychloroquine is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

  Ask your doctor about the risks and benefits of taking this medicine while you are breastfeeding.
- **Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.**
- **Hydroxychloroquine should not be used in children under 6 years.**
- **Hydroxychloroquine should not be used in children over 6 years for long periods.**
- **Do not take this medicine after the expiry date (EXP) printed on the pack.**

  If you take this medicine after the expiry date has passed, it may not work as well.
- **Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.**

  If it has expired or is damaged, return it to your pharmacist for disposal.

Before you start to take it

You must tell your doctor if:

- You are allergic to quinine.
- You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
- You have any pre-existing eye disorders
- You have experienced low blood sugar levels (hypoglycaemia - a "hypo"). Hydroxychloroquine may increase the risk of you having a hypo.
- You have any of these medical conditions:
- chloroquine-resistant malaria
- liver or kidney problems
- diabetes
- stomach, brain or blood disorders
- disease of the heart muscle
- skin diseases, in particular psoriasis which is a kind of itchy rash.
- Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
- Porphyria, which is a rare disease of blood pigments.
- You plan to become pregnant or breastfeed.

If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and hydroxychloroquine may interfere with each other. These include:

- any medicine to treat depression
- digoxin - a medicine used to treat heart disease
- medicines to treat diabetes
- medicines used to suppress the immune system such as cyclosporin
- antiarrythmic drugs such as amiodarone, which control heart rhythm
- other drugs to treat malaria
- medicines to treat epilepsy.

These medicines may be affected by hydroxychloroquine or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Your doctor and pharmacist can tell you if you are taking any of these medicines.

Other interactions not listed above may also occur.

How to take this medicine

Follow all directions given to you by your doctor or pharmacist carefully.

They may be different to the information in this leaflet.

If you do not understand any written instructions, ask your doctor or pharmacist for help.

How much to take

Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.

The dosage will depend on why you are being treated with hydroxychloroquine.

The usual doses are:

Rheumatoid arthritis

Adults

2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE

Adults

2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria Symptoms

Adults

2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria

Adults

The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and 2 further tablets on each of the next two days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for children.

Hydroxychloroquine should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your doctor.

How to take it

Swallow tablets whole with a little water or other liquid.

When to take it

It is best to take hydroxychloroquine at meal times.

How long to take it for

Continue taking your medicine for as long as your doctor tells you.

Make sure you have enough to last over weekends and holidays.

If you forget to take it

- **If you are being given hydroxychloroquine for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.**
- **If you are being given hydroxychloroquine for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.**

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

If you think that you or anyone else may have taken too much of this medicine, immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 in Australia) for advice. Alternatively, go to the Accident and Emergency department at your nearest hospital.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too much hydroxychloroquine, you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While you are taking this medicine

Your doctor will need to perform the following tests during treatment with hydroxychloroquine:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, hydroxychloroquine has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Reactions

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Things you must do

- Tell any other doctors, dentists, and pharmacists who are treating you that you are taking hydroxychloroquine.
- Tell your doctor immediately if you become pregnant.
- If you are about to have any blood tests, tell your doctor that you are taking this medicine.
- Go to your doctor regularly for a check-up.

  Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.
- Tell your doctor if you experience any of the following symptoms including:
  - weakness
  - trembling or shaking
  - sweating
  - light-headedness
  - headache
  - dizziness
  - lack of concentration
  - tearfulness or crying
  - irritability
  - hunger
  - numbness around the lips and fingers.

  These symptoms may be associated with hypoglycaemia.

Treating hypoglycaemia

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets

Unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms.

Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognise the symptoms of hypoglycaemia and know how to treat them.

Things you must not do

- Do not give this medicine to anyone else, even if their symptoms seem similar to yours.
- Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.
- Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of

Be careful while driving or operating machinery until you know how hydroxychloroquine affects you.

Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Hydroxychloroquine may cause hypoglycaemia,which can impair your ability to drive or operate machinery. Make sure you are aware of the symptoms of hypoglycaemia and avoid dangerous activities until your blood sugar returns to normal (see 'Treating hypoglycaemia' under 'Things you must do').

Possible side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking hydroxychloroquine.

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Hydroxychloroquine helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor if you notice any of the following and they worry you:

Stomach problems such as:

- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:

- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking hydroxychloroquine.

Tell your doctor as soon as possible if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:
  - disorientation
  - seizures, fits or convulsions
  - loss of consciousness
- Suicidal behaviour
- Movement problems, such uncontrolled movements, stiffness or tremors
- Wide spread rash with blisters, with or without fever, which can indicate a severe drug induced allergic reaction. It can involve blood changes and internal organs.

These are serious side effects. You may need medical attention.

Serious side effects are rare.

Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell.

Storage and disposal

Storage

Keep your medicine in its original packaging until it is time to take it.

If you take your medicine out of its original packaging it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 25°C.

Do not store your medicine, or any other medicine, in the bathroom or near a sink. Do not leave it on a window sill or in the car. Heat, sunlight and dampness can destroy some medicines.

Keep it where children cannot reach it.

Children are particularly sensitive to the unwanted effects of hydroxychloroquine.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or it has passed its expiry date your pharmacist can dispose of the remaining medicine safely.

Product description

What APO-Hydroxychloroquine looks like

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

* Not all strengths, pack types and/or pack sizes may be available.

Packaged in bottles of 100 tablets.

Ingredients

Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient (equivalent to 155 mg hydroxychloroquine).

It also contains the following inactive ingredients:

- anhydrous calcium hydrogen phosphate
- pregelatinised maize starch
- hypromellose
- magnesium stearate
- polysorbate 80
- colloidal anhydrous silica
- Opadry II White 85F18422.

This medicine is gluten-free, lactose-free and free of other azo dyes.

Australian Registration Numbers

APO-Hydroxychloroquine 200 mg tablets: AUST R 186393.

Sponsor

Apotex Pty Ltd

16 Giffnock Avenue

Macquarie Park NSW 2113

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This leaflet was last updated in:

Oct 2016.

Hydroxychlorouqine GH TABLETS 200 MG

Hydroxychloroquine sulfate 200 mg

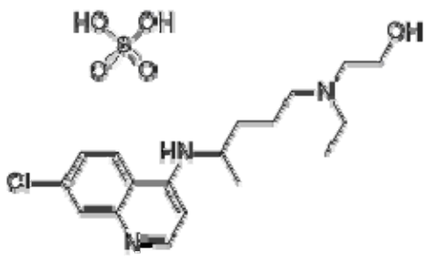
NAME OF THE MEDICINE

AUSTRALIAN APPROVED NAME

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 tablet contains 200 mg hydroxychloroquine sulfate, which is equivalent to 155 mg base. In addition, each tablet contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, pregelatinised maize starch, hypromellose, magnesium stearate, polysorbate 80, colloidal anhydrous silica and Proprietary Ingredient Opadry II White 85F18422.

PHARMACOLOGY

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.

Malaria

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.

Opthamalogical
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. (See adverse reactions section)

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 patents 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.

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 hemorrhages and abnormal retinal pigmentation.

The use of this drug 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.

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 combination 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 level have been reported when cyclosporin and hydroxychloroquine are co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other anitmalarials 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
- *very rare* < 1/10,000 (< 0.01%)

not known frequency cannot be estimated from 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 can occur but is rare. n 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 Disorders

Not known urticaria, angioedema, bronchospasm

Blood Disorders

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

Very rare: agranulocytosis.

Hydroxychloroquine may exacerbate porphyria.

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

Central Nervous System Disorders
Common: affect lability, headache
Uncommon: vertigo, tinnitus, headache, nerve deafness, nervousness, dizziness.
Rare: convulsions, neuromyopathy.
Very rare: psychosis, suicidal behaviour, nightmares, nystagmus, ataxia
Not known hearing loss

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

Gastrointestinal
Very common: abdominal pain, nausea
Common: diarrhoea, vomiting,

Metabolism and nutrition disorders
Common: anorexia
Not known: hypoglycaemia

Liver Disorders
Uncommon: abnormal liver function tests

Very rare: fulminant hepatitis.

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 tendon reflexes and abnormal nerve conduction studies
Very rare: extraocular muscle palsies.

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
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.

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.

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 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 parentally 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

200 mg tablets

White to off-white, capsule-shaped tablets, embossed “HCQS” on one side, plain on the other side.

Packaged in HDPE bottles of 100 tablets

Hydroxychloroquine GH tablets 200 mg are intended for oral administration.

Store below 25°C. Protect from light.

POISON SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR
Ipca Pharma (Australia) Pty Ltd

DATE OF FIRST INCLUSION IN THE ARTG: 2nd February 2015

DATE OF MOST RECENT AMENDMENT*:* January 2015

HYDROXYCHLOROQUINE GH TABLETS 200 MG
CONSUMER MEDICINE INFORMATION

Hydroxychloroquine GH Tablets 200 mg
(Hydroxychloroquine Sulfate 200 mg Film Coated Tablets)

Consumer Medicine Information

What Is In This Leaflet

Read this leaflet carefully before taking your medicine. Ask your doctor or pharmacist if you do not understand anything or are worried about taking your medicine.

This leaflet answers some common questions about hydroxychloroquine. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the last page. Some more recent information on your medicine may be available. Speak to your pharmacist or doctor to obtain the most up-to-date information.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you. Keep this leaflet with your medicine.

You may want to read it again.

What Hydroxychloroquine GH Is Used For

The name of your medicine is Hydroxychloroquine GH Tablets 200 mg. It contains the active ingredient hydroxychloroquine sulfate.

It may be used for any of the following conditions:

Rheumatoid Arthritis
Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain.

Hydroxychloroquine may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, hydroxychloroquine may slow down the process of joint damage and relieve the symptoms of the disease.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)
Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterized by chills, fever and sweats. In malaria, hydroxychloroquine destroys the harmful parasite which causes the illness.

Your doctor may have prescribed hydroxychloroquine for another reason.

Ask your doctor if you have any questions about why this medicine has been prescribed for you. Hydroxychloroquine is not addictive. This medicine is available only with a doctor's prescription.

Before You Take Hydroxychloroquine GH Tablets 200 mg

When you must not take it

Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet.

If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

Symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.

Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.

When hydroxychloroquine is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

Ask your doctor about the risks and benefits of taking this medicine while you are breastfeeding.

Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.

Hydroxychloroquine should not be used in children under 6 years.

Hydroxychloroquine should not be used in children over 6 years for long periods.

Do not take this medicine after the expiry date (EXP) printed on the pack.

It may have no effect at all, or worse, an entirely unexpected effect if you take it after the expiry date.

Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.

Do not take this medicine to treat any other complaint unless your doctor says it is safe.

Do not give this medicine to anyone else.

Before You Start To Take It

You must tell your doctor if:

1. You are allergic to quinine.
2. You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
3. You have any pre-existing eye disorders
4. You have experienced low blood sugar levels (hypoglycaemia – a "hypo"). hydroxychloroquine may increase the risk of you having a hypo.
5. You have or have had any of these medical conditions:
   - Chloroquine-resistant malaria
   - Liver or kidney problems
   - Diabetes
   - Stomach, brain or blood disorders
   - Disease of the heart muscle
   - Skin diseases, in particular psoriasis which is a kind of itchy rash.
   - Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
   - Porphyria, which is a rare disease of blood pigments.
6. You plan to become pregnant or breast-feed.

If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and hydroxychloroquine may interfere with each other. These include:

• Any medicine to treat depression
• Digoxin - a medicine used to treat heart disease
• Medicines to treat diabetes.
• Medicines used to suppress the immune system such as cyclosporin
• Antiarrythmic drugs such as amiodarone
• Other antimalarial drugs
• Medicines to treat epilepsy

These medicines may be affected by hydroxychloroquine or may affect how well it works.
Your doctor and pharmacist can tell you if you are taking any of these medicines.

How To Take Hydroxychloroquine GH Tablets 200 mg

Follow all directions given to you by your doctor or pharmacist carefully.

Swallow tablets whole with a little water or other liquid. It is best to take it at meal times.

How much to take
Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.

The dosage will depend on why you are being treated with hydroxychloroquine.

The usual doses are:

Rheumatoid arthritis
Adults
2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE
Adults
2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria
Symptoms
Adults
2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria
Adults
The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor. Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for you.

Hydroxychloroquine should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your pharmacist or doctor.

How long to take it for
Continue taking your medicine for as long as your doctor tells you. Make sure you have enough to last over weekends and holidays.

If you forget to take it
If you are being given hydroxychloroquine for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given hydroxychloroquine for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 for Australia) for advice, or go to the Accident and Emergency Department at the nearest hospital, if you think that you or anyone else may have taken too much hydroxychloroquine.

Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

If you take too much hydroxychloroquine, you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While You Are Taking Hydroxychloroquine GH Tablets 200 mg

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking hydroxychloroquine.

Tell all doctors, dentists and pharmacists who are treating you that you are taking hydroxychloroquine.

Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers. These symptoms may be associated with hypoglycaemia. If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:
• 5-7 jelly beans
• 3 teaspoons of sugar or honey
• 1/2 can of ordinary (non-diet) soft drink
• 2-3 concentrated glucose tablets
• unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognize the symptoms of hypoglycaemia and know how to treat them. Your doctor will need to perform the following tests during treatment with hydroxychloroquine:

Eye Tests
Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, hydroxychloroquine has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Tests
Your doctor will need to perform occasional blood tests to check for any blood reactions.

Your doctor may monitor your blood sugar levels if you have experienced hypoglycaemia while taking Hydroxychloroquine.

Driving/Operating Machinery
Be careful driving or operating machinery until you know how Hydroxychloroquine affects you. Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to Hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Things you must do
Tell any other doctors, dentists, and pharmacists who are treating you that you are taking Hydroxychloroquine.

Tell your doctor immediately if you become pregnant.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

Go to your doctor regularly for a check-up.

Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.

Things you must not do
Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.

Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of
Be careful while driving or operating machinery until you know how hydroxychloroquine affects you.

Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects of Hydroxychloroquine GH Tablets 200 mg

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking hydroxychloroquine.

Hydroxychloroquine helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor or pharmacist if you notice any of the following and they worry you:

Less serious side effects
Stomach problems such as:
• Nausea
• Vomiting
• Diarrhoea
• Abdominal cramps

Other problems such as:
• Loss of appetite
• Muscle weakness
• Dizziness
• Ringing in the ears
• Headache
• Nervousness
• Skin rash and itching
• Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking hydroxychloroquine.

More serious side effects
Tell your doctor if you notice any of the following:
• Visual disturbances
• Any hearing loss
• Suicidal behaviour
• Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
• More severe symptoms of hypoglycaemia, including:
- disorientation
- seizures, fits or convulsions
- loss of consciousness

These are serious side effects. You may need medical attention.

Serious side effects are rare. Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell

Some people may get other side effects while taking hydroxychloroquine.

After Using Hydroxychloroquine GH Tablets 200 mg

Storage
Keep your medicine in its original packaging until it is time to take it.

If you take your medicine out of its original packaging it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 25°C.

Heat and dampness can destroy some medicines. Do not leave hydroxychloroquine in the car on hot days.

Do not store your medicine, or any other medicine, in the bathroom or near a sink.

Do not leave it on a window sill or in the car.

Heat, sunlight and dampness can destroy some medicines.

Keep it where children cannot reach it.

Children are particularly sensitive to the unwanted effects of hydroxychloroquine.

A locked cupboard at least one-anda- half metres above the ground is a good place to store medicines.

Disposal
If your doctor or pharmacist tells you to stop taking this medicine or it has passed its expiry date, ask your pharmacist what to do with any medicine that is left over.

Where to go for further information
Pharmaceutical companies are not in a position to give people an individual diagnosis or medical advice. Your doctor or pharmacist is the best person to give you advice on the treatment of your condition.

Product Description

What* Hydroxychloroquine GH *Tablets looks like?

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

* Not all strengths, pack types and/or pack sizes may be available.

Packaged in bottles of 100 tablets.

Ingredients
Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient (equivalent to 155 mg hydroxychloroquine).

It also contains the following inactive ingredients:
• anhydrous calcium hydrogen phosphate
• pregelatinised maize starch
• hypromellose
• magnesium stearate
• polysorbate 80
• colloidal anhydrous silica
• Opadry II White 85F18422.

This medicine is gluten-free, lactose free and free of other azo dyes.

Australian Registration Numbers
Hydroxychloroquine GH Tablets 200 mg: 223695

Sponsor
Ipca Pharma (Australia) Pty. Ltd

This leaflet was last updated in: January 2015.

RUSQUEN TABLETS 200 MG

Hydroxychloroquine sulfate 200 mg

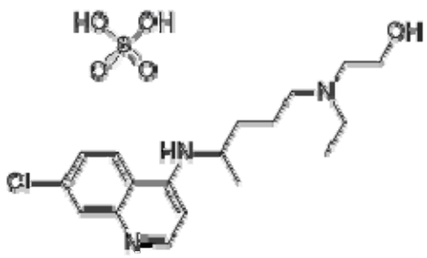
NAME OF THE MEDICINE

AUSTRALIAN APPROVED NAME

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 tablet contains 200 mg hydroxychloroquine sulfate, which is equivalent to 155 mg base. In addition, each tablet contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, pregelatinised maize starch, hypromellose, magnesium stearate, polysorbate 80, colloidal anhydrous silica and Proprietary Ingredient Opadry II White 85F18422.

PHARMACOLOGY

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.

Malaria

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.

Opthamalogical
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. (See adverse reactions section)

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 patents 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.

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 hemorrhages and abnormal retinal pigmentation.

The use of this drug 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.

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 combination 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 level have been reported when cyclosporin and hydroxychloroquine are co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other anitmalarials 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
- *very rare* < 1/10,000 (< 0.01%)

not known frequency cannot be estimated from 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 can occur but is rare. n 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 Disorders

Not known urticaria, angioedema, bronchospasm

Blood Disorders

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

Very rare: agranulocytosis.

Hydroxychloroquine may exacerbate porphyria.

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

Central Nervous System Disorders
Common: affect lability, headache
Uncommon: vertigo, tinnitus, headache, nerve deafness, nervousness, dizziness.
Rare: convulsions, neuromyopathy.
Very rare: psychosis, suicidal behaviour, nightmares, nystagmus, ataxia
Not known hearing loss

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

Gastrointestinal
Very common: abdominal pain, nausea
Common: diarrhoea, vomiting,

Metabolism and nutrition disorders
Common: anorexia
Not known: hypoglycaemia

Liver Disorders
Uncommon: abnormal liver function tests

Very rare: fulminant hepatitis.

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 tendon reflexes and abnormal nerve conduction studies
Very rare: extraocular muscle palsies.

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
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.

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.

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 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 parentally 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

200 mg tablets

White to off-white, capsule-shaped tablets, embossed “HCQS” on one side, plain on the other side.

Packaged in HDPE bottles of 100 tablets

Rusquen tablets 200 mg are intended for oral administration.

Store below 25°C. Protect from light.

POISON SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR
Ipca Pharma (Australia) Pty Ltd

DATE OF FIRST INCLUSION IN THE ARTG: 2nd February 2015

DATE OF MOST RECENT AMENDMENT*:* -

HYDROXYCHLOROQUINE AN TABLETS 200 MG

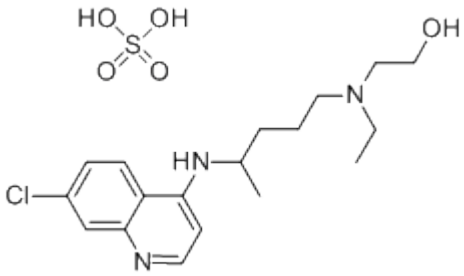
Hydroxychloroquine sulfate 200 mg

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 tablet contains 200 mg hydroxychloroquine sulfate, which is equivalent to 155 mg base. In addition, each tablet contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, pregelatinised maize starch, hypromellose, magnesium stearate, polysorbate 80, colloidal anhydrous silica and Proprietary Ingredient Opadry II White 85F18422.

PHARMACOLOGY

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.

Malaria

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 judgment 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.

Opthamalogical
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. (See adverse reactions section)

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 patents 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.

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 hemorrhages and abnormal retinal pigmentation.

The use of this drug 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.

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 combination 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 level have been reported when cyclosporin and hydroxychloroquine are co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other anitmalarials 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
- *very rare* < 1/10,000 (< 0.01%)

not known frequency cannot be estimated from 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 can occur but is rare. n 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 Disorders
Not known urticaria, angioedema, bronchospasm

Blood Disorders
Rare: bone marrow depression, anaemia, aplastic anaemia, leukopenia, thrombocytopenia.
Very rare: agranulocytosis.
Hydroxychloroquine may exacerbate porphyria.

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

Central Nervous System Disorders
Common: affect lability, headache.
Uncommon: vertigo, tinnitus, headache, nerve deafness, nervousness, dizziness.
Rare: convulsions, neuromyopathy.
Very rare: psychosis, suicidal behaviour, nightmares, nystagmus, ataxia.
Not known: hearing loss.

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

Gastrointestinal
Very common: abdominal pain, nausea.
Common: diarrhoea, vomiting.

Metabolism and nutrition disorders
Common: anorexia.
Not known: hypoglycaemia.

Liver Disorders
Uncommon: abnormal liver function tests

Very rare: fulminant hepatitis.

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 tendon reflexes and abnormal nerve conduction studies.
Very rare: extraocular muscle palsies.

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

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.

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.

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 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 parentally 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

200 mg tablets

White to off-white, capsule-shaped tablets, embossed “HCQS” on one side, plain on the other side.

Packaged in HDPE bottles of 100 tablets

Hydroxychloroquine AN tablets 200 mg are intended for oral administration.

Store below 25°C. Protect from light.

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

Amneal Pharma Australia Pty Ltd
12 River Street
South Yarra
Vic 3141
Australia

DATE OF FIRST INCLUSION IN THE ARTG: 2nd February 2015

DATE OF MOST RECENT AMENDMENT*:* 26th March 2015

HYDROXYCHLOROQUINE AN TABLETS 200 MG CONSUMER MEDICINE INFORMATION

Document 13

Hydroxychloroquine AN
(Hydroxychloroquine Sulfate 200 mg Film Coated Tablets)

Consumer Medicine Information

What Is In This Leaflet

Read this leaflet carefully before taking your medicine. Ask your doctor or pharmacist if you do not understand anything or are worried about taking your medicine.

This leaflet answers some common questions about hydroxychloroquine. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the last page. Some more recent information on your medicine may be available. Speak to your pharmacist or doctor to obtain the most up-to-date information.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

Keep this leaflet with your medicine.
You may want to read it again.

What Hydroxychloroquine AN Is Used For

The name of your medicine is Hydroxychloroquine AN. It contains the active ingredient hydroxychloroquine sulfate.

It may be used for any of the following conditions:

Rheumatoid Arthritis
Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain.

Hydroxychloroquine may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, hydroxychloroquine may slow down the process of joint damage and relieve the symptoms of the disease.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)
Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterized by chills, fever and sweats. In malaria, hydroxychloroquine destroys the harmful parasite which causes the illness.

Your doctor may have prescribed hydroxychloroquine for another reason.

HYDROXYCHLOROQUINE AN TABLETS 200 MG
CONSUMER MEDICINE INFORMATION

Ask your doctor if you have any questions about why this medicine has been prescribed for you. Hydroxychloroquine is not addictive. This medicine is available only with a doctor's prescription.

Before You Take Hydroxychloroquine AN

When you must not take it

Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet. If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.
Symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.

Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.
When hydroxychloroquine is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

Ask your doctor about the risks and benefits of taking this medicine while you are breastfeeding.

Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.

Hydroxychloroquine should not be used in children under 6 years.

Hydroxychloroquine should not be used in children over 6 years for long periods.

Do not take this medicine after the expiry date (EXP) printed on the pack.
It may have no effect at all, or worse, an entirely unexpected effect if you take it after the expiry date.

Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.

Do not take this medicine to treat any other complaint unless your doctor says it is safe.

Do not give this medicine to anyone else.

Before You Start To Take It

You must tell your doctor if:
1. You are allergic to quinine.
2. You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
3. You have any pre-existing eye disorders
4. You have experienced low blood sugar levels (hypoglycaemia – a "hypo"). hydroxychloroquine may increase the risk of you having a hypo.
5. You have or have had any of these medical conditions:
   - Chloroquine-resistant malaria
   - Liver or kidney problems
   - Diabetes
   - Stomach, brain or blood disorders
   - Disease of the heart muscle
   - Skin diseases, in particular psoriasis which is a kind of itchy rash.
   - Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
   - Porphyria, which is a rare disease of blood pigments.
6. You plan to become pregnant or breast-feed.

If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and hydroxychloroquine may interfere with each other. These include:
• Any medicine to treat depression
• Digoxin - a medicine used to treat heart disease
• Medicines to treat diabetes.
• Medicines used to suppress the immune system such as cyclosporine
• Antiarrythmic drugs such as amiodarone
• Other antimalarial drugs
• Medicines to treat epilepsy

These medicines may be affected by hydroxychloroquine or may affect how well it works.
Your doctor and pharmacist can tell you if you are taking any of these medicines.

How To Take Hydroxychloroquine AN

Follow all directions given to you by your doctor or pharmacist carefully.

Swallow tablets whole with a little water or other liquid. It is best to take it at meal times.

How much to take

Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.

The dosage will depend on why you are being treated with hydroxychloroquine.

The usual doses are:

Rheumatoid arthritis
Adults
2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE
Adults
2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria
Symptoms
Adults
2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria
Adults
The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor. Dosages for children are calculated according to the child's body weight.
Your doctor will work out the correct dose for you.

Hydroxychloroquine should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your pharmacist or doctor.

How long to take it for

Continue taking your medicine for as long as your doctor tells you. Make sure you have enough to last over weekends and holidays.

If you forget to take it

If you are being given hydroxychloroquine for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given hydroxychloroquine for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 for Australia) for advice, or go to the Accident and Emergency Department at the nearest hospital, if you think that you or anyone else may have taken too much hydroxychloroquine. Do this even if there are no signs of discomfort or poisoning.
You may need urgent medical attention.

If you take too much hydroxychloroquine, you may experience headaches, drowsiness, visual disturbances or fits. These symptoms may occur within 30 minutes of overdose.

While You Are Taking Hydroxychloroquine AN

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking hydroxychloroquine.

Tell all doctors, dentists and pharmacists who are treating you that you are taking hydroxychloroquine.

Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers.
These symptoms may be associated with hypoglycaemia. If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:
- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets
- unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognize the symptoms of hypoglycaemia and know how to treat them. Your doctor will need to perform the following tests during treatment with hydroxychloroquine:

Eye Tests
Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, hydroxychloroquine has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Tests
Your doctor will need to perform occasional blood tests to check for any blood reactions.

Your doctor may monitor your blood sugar levels if you have experienced hypoglycaemia while taking Hydroxychloroquine.

Driving/Operating Machinery

Be careful driving or operating machinery until you know how Hydroxychloroquine affects you. Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to Hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Things you must do

Tell any other doctors, dentists, and pharmacists who are treating you that you are taking Hydroxychloroquine.

Tell your doctor immediately if you become pregnant.

If you are about to have any blood tests, tell your doctor that you are taking this medicine.

Go to your doctor regularly for a check-up.
Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.

Things you must not do

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.

Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of

Be careful while driving or operating machinery until you know how hydroxychloroquine affects you.

Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects of Hydroxychloroquine AN

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking hydroxychloroquine.
Hydroxychloroquine helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor or pharmacist if you notice any of the following and they worry you:
Less serious side effects
Stomach problems such as:
• Nausea
• Vomiting
• Diarrhoea
• Abdominal cramps

Other problems such as:
• Loss of appetite
• Muscle weakness
• Dizziness
• Ringing in the ears
• Headache
• Nervousness
• Skin rash and itching
• Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking hydroxychloroquine.

More serious side effects
Tell your doctor if you notice any of the following:
• Visual disturbances
• Any hearing loss
• Suicidal behaviour
• Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
• More severe symptoms of hypoglycaemia, including:
- disorientation
- seizures, fits or convulsions
- loss of consciousness

These are serious side effects. You may need medical attention.

Serious side effects are rare. Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell
Some people may get other side effects while taking hydroxychloroquine.

After Using Hydroxychloroquine AN

Storage

Keep your medicine in its original packaging until it is time to take it.
If you take your medicine out of its original packaging it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 25°C.
Heat and dampness can destroy some medicines.

Do not store your medicine, or any other medicine, in the bathroom or near a sink. Do not leave it on a window sill or in the car.
Heat, sunlight and dampness can destroy some medicines.

Keep it where children cannot reach it.
Children are particularly sensitive to the unwanted effects of hydroxychloroquine. A locked cupboard at least one-and-a- half metres above the ground is a good place to store medicines.

Disposal

If your doctor or pharmacist tells you to stop taking this medicine or it has passed its expiry date, ask your pharmacist what to do with any medicine that is left over.

Where to go for further information

Pharmaceutical companies are not in a position to give people an individual diagnosis or medical advice. Your doctor or pharmacist is the best person to give you advice on the treatment of your condition.

HYDROXYCHLOROQUINE AN TABLETS 200 MG
CONSUMER MEDICINE INFORMATION

Product Description

What Hydroxychloroquine AN Tablets looks like?

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

Packaged in bottles of 100 tablets.

Ingredients

Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient (equivalent to 155 mg hydroxychloroquine).

It also contains the following inactive ingredients:
• anhydrous calcium hydrogen phosphate
• pregelatinised maize starch
• hypromellose
• magnesium stearate
• polysorbate 80
• colloidal anhydrous silica
• Opadry II White 85F18422.

This medicine is gluten-free, lactose free and free of other azo dyes.

Australian Registration Numbers

Hydroxychloroquine AN:223694

Sponsor

Amneal Pharma Australia Pty Ltd
12 River Street
South Yarra
Vic 3141
Australia

This leaflet was last updated in: March 2015.

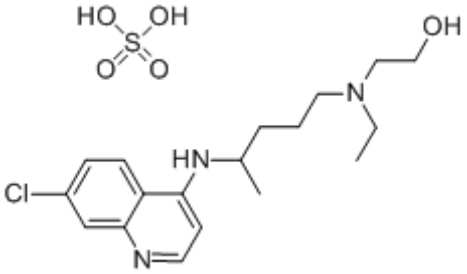
GENRX HYDROXYCHLOROQUINE TABLETS

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 patents 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 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 pustolosis, 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

GenRx 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 186389).

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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

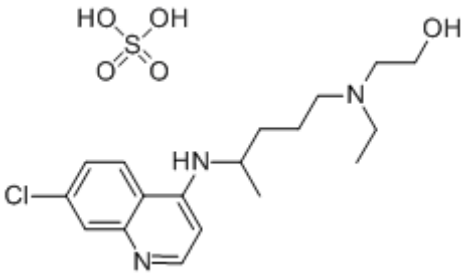
CHEMMART HYDROXYCHLOROQUINE TABLETS

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 patents 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 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 pustolosis, 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

Chemmart 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 186386).

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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

Chemmart Hydroxychloroquine

Contains the active ingredient, hydroxychloroquine sulfate

Consumer Medicine Information

For a copy of a large print leaflet, Ph: 1800 195 055

What is in this leaflet

Read this leaflet carefully before taking your medicine. Ask your doctor or pharmacist if you do not understand anything or are worried about taking your medicine.

This leaflet answers some common questions about hydroxychloroquine.

It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the last page. Some more recent information on your medicine may be available. Speak to your pharmacist or doctor to obtain the most up-to-date information.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

Pharmaceutical companies cannot give you medical advice or an individual diagnosis.

Keep this leaflet with your medicine. You may want to read it again.

What this medicine is used for

The name of your medicine is Chemmart Hydroxychloroquine. It contains the active ingredient hydroxychloroquine sulfate.

It may be used for any of the following conditions:

Rheumatoid Arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain. Hydroxychloroquine may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, hydroxychloroquine may slow down the substances which harm the joints.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterized by chills, fever and sweats.

In malaria, hydroxychloroquine destroys the harmful parasite which causes the illness.

Your doctor may have prescribed hydroxychloroquine for another reason.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

This medicine is available only with a doctor's prescription.

Hydroxychloroquine is not addictive.

Before you take this medicine

When you must not take it

- **Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet.**

  If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

  Symptoms of an allergic reaction may include an asthma attack,

facial swelling, skin rash or hay fever.

- **Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.**

  When hydroxychloroquine is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

  Ask your doctor about the risks and benefits of taking this medicine while you are breastfeeding.
- **Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.**
- **Hydroxychloroquine should not be used in children under 6 years.**
- **Hydroxychloroquine should not be used in children over 6 years for long periods.**
- **Do not take this medicine after the expiry date (EXP) printed on the pack.**

  If you take this medicine after the expiry date has passed, it may not work as well.
- **Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.**

  If it has expired or is damaged, return it to your pharmacist for disposal.

Before you start to take it

You must tell your doctor if:

- You are allergic to quinine.
- You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
- You have any pre-existing eye disorders
- You have experienced low blood sugar levels (hypoglycaemia - a "hypo"). Hydroxychloroquine may increase the risk of you having a hypo.
- You have any of these medical conditions:
- chloroquine-resistant malaria
- liver or kidney problems
- diabetes
- stomach, brain or blood disorders
- disease of the heart muscle
- skin diseases, in particular psoriasis which is a kind of itchy rash.
- Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
- Porphyria, which is a rare disease of blood pigments.
- You plan to become pregnant or breastfeed.

If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and hydroxychloroquine may interfere with each other. These include:

- any medicine to treat depression
- digoxin - a medicine used to treat heart disease
- medicines to treat diabetes
- medicines used to suppress the immune system such as cyclosporin
- antiarrythmic drugs such as amiodarone, which control heart rhythm
- other drugs to treat malaria
- medicines to treat epilepsy.

These medicines may be affected by hydroxychloroquine or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Your doctor and pharmacist can tell you if you are taking any of these medicines.

Other interactions not listed above may also occur.

How to take this medicine

Follow all directions given to you by your doctor or pharmacist carefully.

They may be different to the information in this leaflet.

If you do not understand any written instructions, ask your doctor or pharmacist for help.

How much to take

Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.

The dosage will depend on why you are being treated with hydroxychloroquine.

The usual doses are:

Rheumatoid arthritis

Adults

2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE

Adults

2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria Symptoms

Adults

2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria

Adults

The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and 2 further tablets on each of the next two days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for children.

Hydroxychloroquine should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your doctor.

How to take it

Swallow tablets whole with a little water or other liquid.

When to take it

It is best to take hydroxychloroquine at meal times.

How long to take it for

Continue taking your medicine for as long as your doctor tells you.

Make sure you have enough to last over weekends and holidays.

If you forget to take it

- **If you are being given hydroxychloroquine for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.**
- **If you are being given hydroxychloroquine for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.**

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

If you think that you or anyone else may have taken too much of this medicine, immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 in Australia) for advice. Alternatively, go to the Accident and Emergency department at your nearest hospital.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too much hydroxychloroquine, you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While you are taking this medicine

Your doctor will need to perform the following tests during treatment with hydroxychloroquine:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, hydroxychloroquine has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Reactions

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Things you must do

- Tell any other doctors, dentists, and pharmacists who are treating you that you are taking hydroxychloroquine.
- Tell your doctor immediately if you become pregnant.
- If you are about to have any blood tests, tell your doctor that you are taking this medicine.
- Go to your doctor regularly for a check-up.

  Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.
- Tell your doctor if you experience any of the following symptoms including:
  - weakness
  - trembling or shaking
  - sweating
  - light-headedness
  - headache
  - dizziness
  - lack of concentration
  - tearfulness or crying
  - irritability
  - hunger
  - numbness around the lips and fingers.

  These symptoms may be associated with hypoglycaemia.

Treating hypoglycaemia

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets

Unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms.

Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognise the symptoms of hypoglycaemia and know how to treat them.

Things you must not do

- Do not give this medicine to anyone else, even if their symptoms seem similar to yours.
- Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.
- Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of

Be careful while driving or operating machinery until you know how hydroxychloroquine affects you.

Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Hydroxychloroquine may cause hypoglycaemia,which can impair your ability to drive or operate machinery. Make sure you are aware of the symptoms of hypoglycaemia and avoid dangerous activities until your blood sugar returns to normal (see 'Treating hypoglycaemia' under 'Things you must do').

Possible side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking hydroxychloroquine.

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Hydroxychloroquine helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor if you notice any of the following and they worry you:

Stomach problems such as:

- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:

- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking hydroxychloroquine.

Tell your doctor as soon as possible if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:
  - disorientation
  - seizures, fits or convulsions
  - loss of consciousness
- Suicidal behaviour
- Movement problems, such uncontrolled movements, stiffness or tremors
- Wide spread rash with blisters, with or without fever, which can indicate a severe drug induced allergic reaction. It can involve blood changes and internal organs.

These are serious side effects. You may need medical attention.

Serious side effects are rare.

Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell.

Storage and disposal

Storage

Keep your medicine in its original packaging until it is time to take it.

If you take your medicine out of its original packaging it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 25°C.

Do not store your medicine, or any other medicine, in the bathroom or near a sink. Do not leave it on a window sill or in the car. Heat, sunlight and dampness can destroy some medicines.

Keep it where children cannot reach it.

Children are particularly sensitive to the unwanted effects of hydroxychloroquine.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or it has passed its expiry date your pharmacist can dispose of the remaining medicine safely.

Product description

What Chemmart Hydroxychloroquine looks like

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

* Not all strengths, pack types and/or pack sizes may be available.

Packaged in bottles of 100 tablets.

Ingredients

Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient (equivalent to 155 mg hydroxychloroquine).

It also contains the following inactive ingredients:

- anhydrous calcium hydrogen phosphate
- pregelatinised maize starch
- hypromellose
- magnesium stearate
- polysorbate 80
- colloidal anhydrous silica
- Opadry II White 85F18422.

This medicine is gluten-free, lactose-free and free of other azo dyes.

Australian Registration Numbers

Chemmart Hydroxychloroquine 200 mg tablets: AUST R 186386.

Sponsor

Apotex Pty Ltd

16 Giffnock Avenue

Macquarie Park NSW 2113

This leaflet was last updated in:

Oct 2016.

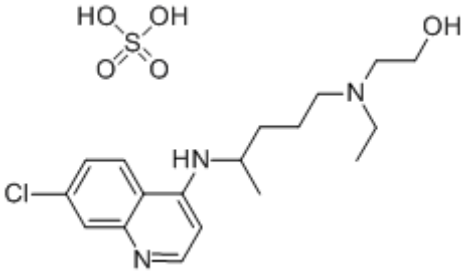
APOTEX- HYDROXYCHLOROQUINE TABLETS

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 patents 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 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 pustolosis, 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

APOTEX 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 186387).

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

APO and APOTEX are registered trade marks of Apotex Inc.

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

PRODUCT INFORMATION

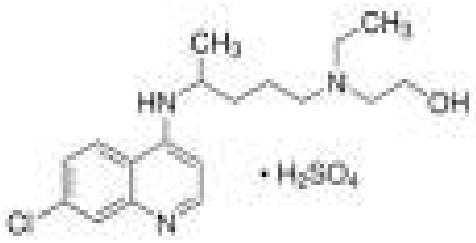
HYDROXYCHLOROQUINE RBX
hydroxychloroquine sulfate 200 mg tablets

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 tablet contains 200 mg hydroxychloroquine sulfate, which is equivalent to 155 mg base. In addition, each tablet contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, pregelatinised maize starch, hypromellose, magnesium stearate, polysorbate 80, colloidal anhydrous silica and OPADRY II complete film coating system 85F18422 White (PI # 11376).

PHARMACOLOGY

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.

Malaria

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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.

Opthamalogical 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.

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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.

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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.

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 hemorrhages and abnormal retinal pigmentation.

The use of this drug 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.

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 level have been reported when cyclosporin and hydroxychloroquine are co-administered.

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

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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
- *very rare* < 1/10,000 (< 0.01%)
- *not known* frequency cannot be estimated from 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 can occur but is rare. 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 and bronchospasm

Blood Disorders

Rare: bone marrow depression, anaemia, aplastic anaemia, leukopenia, thrombocytopenia.
Very rare: agranulocytosis.
Hydroxychloroquine may exacerbate porphyria.

Cardiovascular Disorders

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

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

Dermatological

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

Gastrointestinal

Very Common: nausea, abdominal pain.
Common: diarrhoea, vomiting.

Metabolism and nutrition disorders

Common: anorexia
Not known: hypoglycaemia

Liver Disorders

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

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 tendon reflexes and abnormal nerve conduction studies.
Very rare: extraocular muscle palsies.

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

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.

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.

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 parentally 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

200 mg tablets

White to off-white, capsule-shaped tablets, embossed “HCQS” on one side, plain on the other side.

Each tablet contains 200 mg hydroxycholoroquine sulfate equivalent to 155 mg base.

Packaged in HDPE bottles of 100 tablets (AUST R 186392).

HYDROXYCHLOROQUINE RBX tablets are intended for oral administration.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Ranbaxy Australia Pty Ltd.
9-13 Waterloo Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

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

13 April 2012

DATE OF MOST RECENT AMENDMENT:

20 April 2015

HYDROXYCHLOROQUINE RBX

hydroxychloroquine sulfate 200 mg tablets

Consumer Medicine Information

What Is In This Leaflet

Read this leaflet carefully before taking your medicine. Ask your doctor or pharmacist if you do not understand anything or are worried about taking your medicine.
This leaflet answers some common questions about HYDROXYCHLOROQUINE RBX. It does not contain all the available Information.
It does not take the place of talking to your doctor or pharmacist.
This leaflet was last updated on the date at the end of this leaflet. More recent information may be available. The latest Consumer Medicine Information is available from https://www.ebs.tga.gov.au/ and may contain important information about the medicine and its use of which you should be aware.
All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you. Keep this leaflet with your medicine.
You may want to read it again.

What HYDROXYCHLOROQUINE RBX Is Used For

The name of your medicine is HYDROXYCHLOROQUINE RBX. It contains the active ingredient hydroxychloroquine sulfate.
It may be used for any of the following conditions:

Rheumatoid Arthritis
Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain.
HYDROXYCHLOROQUINE RBX may be used for short or long-term rheumatoid arthritis treatment.
In treating rheumatoid arthritis, HYDROXYCHLOROQUINE RBX may slow down the substances which harm the joints.

Systemic Lupus Erythematous (SLE)
SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.
These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)
DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)
Malaria is an infectious disease caused by the presence of parasites in red blood cells.
The disease is characterized by chills, fever and sweats. In malaria, HYDROXYCHLOROQUINE RBX destroys the harmful parasite which causes the illness.
Your doctor may have prescribed HYDROXYCHLOROQUINE RBX for another reason.
Ask your doctor if you have any questions about why this medicine has been prescribed for you.
5.
HYDROXYCHLOROQUINE RBX is not addictive. This medicine is available only with a doctor's prescription.

Before You Take HYDROXYCHLOROQUINE RBX

When you must not take it
Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet.
If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.
Symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.
Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.
When HYDROXYCHLOROQUINE RBX is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.
Ask your doctor about the risks and benefits of taking this medicine while you are breastfeeding.
Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.
HYDROXYCHLOROQUINE RBX should not be used in children under 6 years.
HYDROXYCHLOROQUINE RBX should not be used in children over 6 years for long periods.
Do not take this medicine after the expiry date (EXP) printed on the pack.
If you take this medicine after the expiry date has passed, it may not work as well.
Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.
If it has expired or is damaged, return it to your pharmacist for disposal.
If you are not sure whether you should start taking this medicine, talk to your doctor or pharmacist.
Do not take this medicine to treat any other complaint unless your doctor says it is safe.
Do not give this medicine to anyone else.

Before you start to take it
You must tell your doctor if:
1. You are allergic to quinine.
2. You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
3. You have any pre-existing eye disorders
4. You have experienced low blood sugar levels (Hypoglycaemia or hypo). Hydroxychloroquine RBX may increase the risk of you having a hypo
5. You have any of these medical conditions:
• Chloroquine-resistant malaria
• Liver or kidney problems
• Diabetes
• Stomach, brain or blood disorders
• Skin diseases, in particular psoriasis which is a kind of itchy rash.
• Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
• Porphyria, which is a rare disease of blood pigments.
You plan to become pregnant or breast-feed.
If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines
Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.
Some medicines and HYDROXYCHLOROQUINE RBX may interfere with each other. These include:
• Any medicine to treat depression
• Digoxin - a medicine used to treat heart disease
• Medicines to treat diabetes.
• Medicines used to suppress the immune system such as cyclosporine
• Antiarrhythmic drugs such as amiodarone
• Other antimalarial drugs
• Medicines to treat epilepsy
These medicines may be affected by HYDROXYCHLOROQUINE RBX or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.
Your doctor and pharmacist can tell you if you are taking any of these medicines. They may also have more Information on medicines to be careful with or avoid while taking HYDROXYCHLOROQUINE RBX.
Other interactions not listed above may also occur.

How to take HYDROXYCHLOROQUINE RBX

Follow all directions given to you by your doctor or pharmacist carefully.
They may be different to the information in this leaflet.
If you do not understand any written instructions, ask your doctor or pharmacist for help.

How much to take
Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.
The dosage will depend on why you are being treated with HYDROXYCHLOROQUINE RBX.

The usual doses are:
Rheumatoid arthritis
Adults
2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE
Adults
2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria
Symptoms
Adults
2 tablets once a week. The tablets should be taken on exactly the same day of each week.
For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria
Adults
The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor. Dosages for children are calculated according to the child's body weight.
Your doctor will work out the correct dose for you.
HYDROXYCHLOROQUINE RBX should not be used in children for long periods.
Your doctor may ask you to take a different dose. You should follow the instructions on the label.
If you are unsure what dose to take ask your pharmacist or doctor.

How to take it
Swallow tablets whole with a little water or other liquid.

When to take it
It is best to take HYDROXYCHLOROQUINE RBX at meal times.

How long to take it for
Continue taking your medicine for as long as your doctor tells you. Make sure you have enough to last over weekends and holidays.

If you forget to take it
If you are being given HYDROXYCHLOROQUINE RBX for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given HYDROXYCHLOROQUINE RBX for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)
Immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 for Australia) for advice, or go to the Accident and Emergency Department at the nearest hospital, if you think that you or anyone else may have taken too much HYDROXYCHLOROQUINE RBX.
Do this even if there are no signs of discomfort or poisoning.
You may need urgent medical attention.
If you take too much HYDROXYCHLOROQUINE RBX, you may experience headaches, drowsiness, visual disturbances or fits.
These symptoms may occur within 30 minutes of overdose.

While You Are Taking HYDROXYCHLOROQUINE RBX

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking HYDROXYCHLOROQUINE RBX.
Tell all doctors, dentists and pharmacists who are treating you that you are taking HYDROXYCHLOROQUINE RBX.
Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers.
These symptoms may be associated with hypoglycaemia.

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently.

You can do this by taking one of the following:
- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets
- unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognize the symptoms of hypoglycaemia and know how to treat them.

Your doctor will need to perform the following tests during treatment with HYDROXYCHLOROQUINE RBX

Your doctor may monitor your blood sugar levels if you have experienced hypoglycaemia while taking hydroxychloroquine

Eye Tests
Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, HYDROXYCHLOROQUINE RBX has been associated with blindness. This can be avoided by having regular eye tests.
It is recommended you wear sunglasses when out in the sun.

Blood Reactions
Your doctor will need to perform occasional blood tests to check for any blood reactions.

Things you must do
Tell any other doctors, dentists, and pharmacists who are treating you that you are taking HYDROXYCHLOROQUINE RBX.
Tell your doctor immediately if you become pregnant.
If you are about to have any blood tests, tell your doctor that you are taking this medicine.
Go to your doctor regularly for a check-up.
Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.

Things you must not do
Do not give this medicine to anyone else, even if their symptoms seem similar to yours.
Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.
Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of
Be careful while driving or operating machinery until you know how HYDROXYCHLOROQUINE RBX affects you.
HYDROXYCHLOROQUINE RBX may cause problems with the eyesight of some people. Make sure you know how you react to HYDROXYCHLOROQUINE RBX before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking HYDROXYCHLOROQUINE RBX.

HYDROXYCHLOROQUINE RBX helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor or pharmacist if you notice any of the following and they worry you:

Less serious side effects
Stomach problems such as:
- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:
- Muscle weakness
- Loss of appetite
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking HYDROXYCHLOROQUINE RBX.

More serious side effects
Tell your doctor if you notice any of the following:
- Visual disturbances
- Any hearing loss
- Suicidial behaviour
- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia including
  - Disorientation
  - Seizures, fits or convulsions
  - Loss of consciousness

These are serious side effects. You may need medical attention.
Serious side effects are rare. Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell

After Using HYDROXYCHLOROQUINE RBX

Storage

Keep your medicine in its original packaging until it is time to take it.
If you take your medicine out of its original packaging it may not keep well.
Keep your medicine in a cool dry place where the temperature will stay below 25°C.

Do not store your medicine, or any other medicine, in the bathroom or near a sink.
Do not leave it on a window sill or in the car.
Heat, sunlight and dampness can destroy some medicines.
Keep it where children cannot reach it
Children are particularly sensitive to the unwanted effects of HYDROXYCHLOROQUINE RBX.
A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor or pharmacist tells you to stop taking this medicine or it has passed its expiry date, ask your pharmacist what to do with any medicine that is left over.

Where to go for further information

Pharmaceutical companies are not in a position to give people an individual diagnosis or medical advice. Your doctor or pharmacist is the best person to give you advice on the treatment of your condition.

Product Description

What HYDROXYCHLOROQUINE RBX looks like

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

Packaged in bottles of 100 tablets.

Ingredients

Active ingredient:
Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient.

Inactive ingredients:
- anhydrous calcium hydrogen phosphate
- pregelatinised maize starch
- hypromellose
- magnesium stearate
- polysorbate 80
- colloidal anhydrous silica
- OPADRY II complete film coating system 85F18422 White.

This medicine does not contain gluten or lactose.

Sponsor

Ranbaxy Australia Pty Ltd.
9-13 Waterloo Road
Macquarie Park NSW 2113

Australian Registration Numbers

HYDROXYCHLOROQUINE RBX 200 mg tablets: AUST R 186392.

This leaflet was prepared in April 2015.

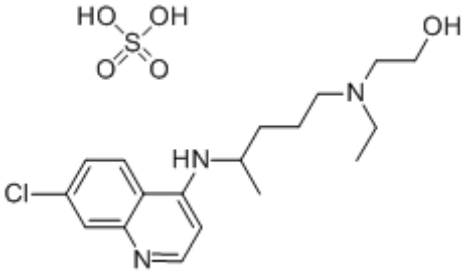
TERRY WHITE CHEMISTS HYDROXYCHLOROQUINE TABLETS

NAME OF THE MEDICINE

Hydroxychloroquine sulfate.

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

Structural Formula:



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

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 patents 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* ≥ 1/10 (≥ 10%)
- *common* ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
- *uncommon* ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
- *rare* ≥ 1/10,000 and < 1/1000 (≥ 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 pustolosis, 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 overdosage.

PRESENTATION AND STORAGE CONDITIONS

Terry White Chemist 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 186391).

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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

Terry White Chemists Hydroxychloroquine

Contains the active ingredient, hydroxychloroquine sulfate

Consumer Medicine Information

For a copy of a large print leaflet, Ph: 1800 195 055

What is in this leaflet

Read this leaflet carefully before taking your medicine. Ask your doctor or pharmacist if you do not understand anything or are worried about taking your medicine.

This leaflet answers some common questions about hydroxychloroquine.

It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the last page. Some more recent information on your medicine may be available. Speak to your pharmacist or doctor to obtain the most up-to-date information.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

Pharmaceutical companies cannot give you medical advice or an individual diagnosis.

Keep this leaflet with your medicine. You may want to read it again.

What this medicine is used for

The name of your medicine is Terry White Chemists Hydroxychloroquine. It contains the active ingredient hydroxychloroquine sulfate.

It may be used for any of the following conditions:

Rheumatoid Arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterized by stiffness, swelling and pain. Hydroxychloroquine may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, hydroxychloroquine may slow down the substances which harm the joints.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterized by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterized by chills, fever and sweats.

In malaria, hydroxychloroquine destroys the harmful parasite which causes the illness.

Your doctor may have prescribed hydroxychloroquine for another reason.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

This medicine is available only with a doctor's prescription.

Hydroxychloroquine is not addictive.

Before you take this medicine

When you must not take it

- **Do not take this medicine if you have had an allergic reaction to hydroxychloroquine, chloroquine or related products or any of the ingredients listed at the end of this leaflet.**

  If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

  Symptoms of an allergic reaction may include an asthma attack,

facial swelling, skin rash or hay fever.

- **Ask your doctor about the risks and benefits of taking this medicine while you are pregnant.**

  When hydroxychloroquine is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

  Ask your doctor about the risks and benefits of taking this medicine while you are breastfeeding.
- **Do not take this medicine if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.**
- **Hydroxychloroquine should not be used in children under 6 years.**
- **Hydroxychloroquine should not be used in children over 6 years for long periods.**
- **Do not take this medicine after the expiry date (EXP) printed on the pack.**

  If you take this medicine after the expiry date has passed, it may not work as well.
- **Do not take this medicine if the packaging is torn, shows signs of tampering or if it does not look quite right.**

  If it has expired or is damaged, return it to your pharmacist for disposal.

Before you start to take it

You must tell your doctor if:

- You are allergic to quinine.
- You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
- You have any pre-existing eye disorders
- You have experienced low blood sugar levels (hypoglycaemia - a "hypo"). Hydroxychloroquine may increase the risk of you having a hypo.
- You have any of these medical conditions:
- chloroquine-resistant malaria
- liver or kidney problems
- diabetes
- stomach, brain or blood disorders
- disease of the heart muscle
- skin diseases, in particular psoriasis which is a kind of itchy rash.
- Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
- Porphyria, which is a rare disease of blood pigments.
- You plan to become pregnant or breastfeed.

If you have not told your doctor about any of the above, tell them before you start taking this medicine.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and hydroxychloroquine may interfere with each other. These include:

- any medicine to treat depression
- digoxin - a medicine used to treat heart disease
- medicines to treat diabetes
- medicines used to suppress the immune system such as cyclosporin
- antiarrythmic drugs such as amiodarone, which control heart rhythm
- other drugs to treat malaria
- medicines to treat epilepsy.

These medicines may be affected by hydroxychloroquine or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Your doctor and pharmacist can tell you if you are taking any of these medicines.

Other interactions not listed above may also occur.

How to take this medicine

Follow all directions given to you by your doctor or pharmacist carefully.

They may be different to the information in this leaflet.

If you do not understand any written instructions, ask your doctor or pharmacist for help.

How much to take

Your doctor or pharmacist will tell you how many tablets you will need to take. This depends on your condition and whether or not you are taking any other medicines.

The dosage will depend on why you are being treated with hydroxychloroquine.

The usual doses are:

Rheumatoid arthritis

Adults

2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE

Adults

2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria Symptoms

Adults

2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of Malaria

Adults

The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and 2 further tablets on each of the next two days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for children.

Hydroxychloroquine should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your doctor.

How to take it

Swallow tablets whole with a little water or other liquid.

When to take it

It is best to take hydroxychloroquine at meal times.

How long to take it for

Continue taking your medicine for as long as your doctor tells you.

Make sure you have enough to last over weekends and holidays.

If you forget to take it

- **If you are being given hydroxychloroquine for rheumatoid arthritis or SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.**
- **If you are being given hydroxychloroquine for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.**

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

If you think that you or anyone else may have taken too much of this medicine, immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 in Australia) for advice. Alternatively, go to the Accident and Emergency department at your nearest hospital.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too much hydroxychloroquine, you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While you are taking this medicine

Your doctor will need to perform the following tests during treatment with hydroxychloroquine:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, hydroxychloroquine has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Reactions

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Things you must do

- Tell any other doctors, dentists, and pharmacists who are treating you that you are taking hydroxychloroquine.
- Tell your doctor immediately if you become pregnant.
- If you are about to have any blood tests, tell your doctor that you are taking this medicine.
- Go to your doctor regularly for a check-up.

  Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.
- Tell your doctor if you experience any of the following symptoms including:
  - weakness
  - trembling or shaking
  - sweating
  - light-headedness
  - headache
  - dizziness
  - lack of concentration
  - tearfulness or crying
  - irritability
  - hunger
  - numbness around the lips and fingers.

  These symptoms may be associated with hypoglycaemia.

Treating hypoglycaemia

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets

Unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms.

Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognise the symptoms of hypoglycaemia and know how to treat them.

Things you must not do

- Do not give this medicine to anyone else, even if their symptoms seem similar to yours.
- Do not take your medicine to treat any other complaints unless your doctor or pharmacist tells you to.
- Do not stop taking your medicine, or change the dosage, without checking with your doctor.

Things to be careful of

Be careful while driving or operating machinery until you know how hydroxychloroquine affects you.

Hydroxychloroquine may cause problems with the eyesight of some people. Make sure you know how you react to hydroxychloroquine before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Hydroxychloroquine may cause hypoglycaemia,which can impair your ability to drive or operate machinery. Make sure you are aware of the symptoms of hypoglycaemia and avoid dangerous activities until your blood sugar returns to normal (see 'Treating hypoglycaemia' under 'Things you must do').

Possible side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking hydroxychloroquine.

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time, they are not. Your doctor has weighed the risks of using this medicine against the benefits they expect it will have for you.

Hydroxychloroquine helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria symptoms, but it may have unwanted side effects in a few people.

You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Following is a list of possible side effects. Do not be alarmed by this list. You may not experience any of them.

Tell your doctor if you notice any of the following and they worry you:

Stomach problems such as:

- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:

- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking hydroxychloroquine.

Tell your doctor as soon as possible if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:
  - disorientation
  - seizures, fits or convulsions
  - loss of consciousness
- Suicidal behaviour
- Movement problems, such uncontrolled movements, stiffness or tremors
- Wide spread rash with blisters, with or without fever, which can indicate a severe drug induced allergic reaction. It can involve blood changes and internal organs.

These are serious side effects. You may need medical attention.

Serious side effects are rare.

Other side effects not listed above may occur in some patients.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell.

Storage and disposal

Storage

Keep your medicine in its original packaging until it is time to take it.

If you take your medicine out of its original packaging it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 25°C.

Do not store your medicine, or any other medicine, in the bathroom or near a sink. Do not leave it on a window sill or in the car. Heat, sunlight and dampness can destroy some medicines.

Keep it where children cannot reach it.

Children are particularly sensitive to the unwanted effects of hydroxychloroquine.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or it has passed its expiry date your pharmacist can dispose of the remaining medicine safely.

Product description

What Terry White Chemists Hydroxychloroquine looks like

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

* Not all strengths, pack types and/or pack sizes may be available.

Packaged in bottles of 100 tablets.

Ingredients

Each tablet contains 200 mg of hydroxychloroquine sulfate as the active ingredient (equivalent to 155 mg hydroxychloroquine).

It also contains the following inactive ingredients:

- anhydrous calcium hydrogen phosphate
- pregelatinised maize starch
- hypromellose
- magnesium stearate
- polysorbate 80
- colloidal anhydrous silica
- Opadry II White 85F18422.

This medicine is gluten-free, lactose-free and free of other azo dyes.

Australian Registration Numbers

Terry White Chemists Hydroxychloroquine 200 mg tablets: AUST R 186391.

Sponsor

Apotex Pty Ltd

16 Giffnock Avenue

Macquarie Park NSW 2113

This leaflet was last updated in:

Oct 2016.

PRODUCT INFORMATION

HYDROXYCHLOROQUINE WINTHROP

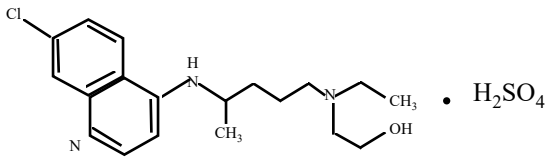
NAME OF MEDICINE

AUSTRALIAN APPROVED NAME

Hydroxychloroquine sulfate

CHEMICAL STRUCTURE

Hydroxychloroquine sulfate is designated chemically as 2 {N (4-(7-Chloro-4-quinolylamino)pentyl)- -N-ethylamino}ethanol sulfate, and has the following chemical structure:



$C_{18}H_{26}ClN_3O$, H_2SO_4 Molecular Weight: 433.96

CAS REGISTRY NUMBER

747-36-4 (hydroxychloroquine sulfate)
118-42-3 (hydroxychloroquine).

DESCRIPTION

Film coated tablets containing hydroxychloroquine sulfate 200 mg (equivalent to 155 mg base). The tablets also contain the inactive ingredients calcium hydrogen phosphate, maize starch, purified water, and magnesium stearate. The film coating contains small amounts of hypromellose, macrogol 400, titanium dioxide, polysorbate 80, carnauba wax, black ink (Tekprint SB-9014SD), and purified water.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

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

Malaria

Like chloroquine phosphate, Hydroxychloroquine Winthrop is highly 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 Winthrop 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 Winthrop is contraindicated in:

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

PRECAUTIONS

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

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

Hydroxychloroquine Winthrop 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, the drug should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Hydroxychloroquine Winthrop 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 Winthrop. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Hydroxychloroquine Winthrop 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

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, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy. (See adverse reactions section)

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 per kg body weight per day.

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

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used 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 patents 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 Winthrop 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, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, Hydroxychloroquine Winthrop 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 this preparation 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, the drug should be discontinued. Safe use of the drug 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 this drug 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.

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 anitmalarials 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*	≥ 1/10 (≥ 10%)
	common	≥ 1/100 and < 1/10 (≥ 1% and <10%)
	uncommon	≥1/1000 and < 1/100 (≥ 0.1% and <1.0%)
	rare	≥1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	very rare	< 1/10,000 (< 0.01%)
	not known	frequency cannot be estimated from 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 Winthrop, 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 Winthrop. 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 six-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 Winthrop; 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, leucopenia, thrombocytopenia

Very rare: agranulocytosis

Hydroxychloroquine may exacerbate porphyria

Central Nervous System

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 tendon reflexes and abnormal nerve conduction studies

Very rare: extraocular muscle palsies

Gastrointestinal

Very common: abdominal pain, nausea

Common: diarrhoea, 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 generalised exanthematous pustolosis (AGEP), 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 Winthrop 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 to 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 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 dose can be reduced to 200 to 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 Winthrop for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Hydroxychloroquine Winthrop 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 methylprednisolone from 1 to 2 mg and dexamethasone from 0.25 to 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, the antimalarials are the drugs of choice.

The dosage of Hydroxychloroquine Winthrop 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 Winthrop 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 Winthrop 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 in six to eight hours and 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 the 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.

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

White to off-white peanut shaped tablets marked “HCQ 200" in black ink on one face of the tablet. Hydroxychloroquine Winthrop is supplied as 100 tablets in an HDPE bottle.

Hydroxychloroquine Winthrop tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

19 August 1994

DATE OF MOST RECENT AMENDMENT

18 September 2015

PRODUCT INFORMATION

HYDROXYCHLOROQUINE WINTHROP

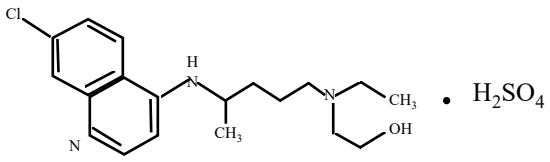
NAME OF MEDICINE

AUSTRALIAN APPROVED NAME

Hydroxychloroquine sulfate

CHEMICAL STRUCTURE

Hydroxychloroquine sulfate is designated chemically as 2 {N (4-(7-Chloro-4-quinolylamino)pentyl)- -N-ethylamino}ethanol sulfate, and has the following chemical structure:



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118-42-3 (hydroxychloroquine).

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PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

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

Malaria

Like chloroquine phosphate, Hydroxychloroquine Winthrop is highly 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 Winthrop 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 Winthrop is contraindicated in:

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

PRECAUTIONS

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

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

Hydroxychloroquine Winthrop 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, the drug should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Hydroxychloroquine Winthrop 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 Winthrop. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Hydroxychloroquine Winthrop 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

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. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity.

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, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy. (See adverse reactions section)

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

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 per kg body weight per day.

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

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used 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 patents 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 Winthrop 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, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, Hydroxychloroquine Winthrop 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 this preparation 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, the drug should be discontinued. Safe use of the drug 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. Hydroxychloroquine should be avoided in pregnancy except when, in the judgement of the physician, the potential benefits outweigh the potential hazards.

The use of this drug 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.

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 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.

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*	≥ 1/10 (≥ 10%)
	common	≥ 1/100 and < 1/10 (≥ 1% and <10%)
	uncommon	≥1/1000 and < 1/100 (≥ 0.1% and <1.0%)
	rare	≥1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	very rare	< 1/10,000 (< 0.01%)
	not known	frequency cannot be estimated from 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 Winthrop, 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 Winthrop. 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 six-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 Winthrop; 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, leucopenia, thrombocytopenia

Very rare: agranulocytosis

Hydroxychloroquine may exacerbate porphyria

Central Nervous System

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 tendon reflexes and abnormal nerve conduction studies

Very rare: extraocular muscle palsies

Gastrointestinal

Very common: abdominal pain, nausea

Common: diarrhoea, 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)

Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed.

Dermatological

Common: skin rashes, alopecia, pruritus

Uncommon: pigmentary changes, bleaching of hair

Very rare: acute generalised exanthematous pustolosis (AGEP), 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 Winthrop 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 to 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 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 dose can be reduced to 200 to 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 Winthrop for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Hydroxychloroquine Winthrop 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 methylprednisolone from 1 to 2 mg and dexamethasone from 0.25 to 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, the antimalarials are the drugs of choice.

The dosage of Hydroxychloroquine Winthrop 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 Winthrop 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 Winthrop 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 in six to eight hours and 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 the 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.

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

White to off-white peanut shaped tablets marked “HCQ 200" in black ink on one face of the tablet. Hydroxychloroquine Winthrop is supplied as 100 tablets in an HDPE bottle.

Hydroxychloroquine Winthrop tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

19 August 1994

DATE OF MOST RECENT AMENDMENT

20 February 2017

Hydroxychloroquine Winthrop Tablets

hydroxychloroquine sulfate

Consumer Medicine Information (CMI)

Please read this leaflet before you start to take this medicine.

What is in this leaflet

This leaflet answers some common questions about Hydroxychloroquine Winthrop Tablets. It does not contain all the available information.

It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. In deciding to give you Hydroxychloroquine Winthrop , your doctor has weighed the risks of taking Hydroxychloroquine Winthrop against the benefits it will have for you.

Keep this information with the tablets. You may wish to read it again later.

What is Hydroxychloroquine Winthrop used for

Hydroxychloroquine Winthrop may be used for any of the following conditions:

Rheumatoid arthritis

Rheumatoid arthritis is a form of arthritis with inflammation of the joints, characterised by stiffness, swelling and pain.
Hydroxychloroquine Winthrop may be used for short or long-term rheumatoid arthritis treatment.

In treating rheumatoid arthritis, Hydroxychloroquine Winthrop may slow down the process of joint damage and relieve the symptoms of the disease.

Systemic Lupus Erythematous (SLE)

SLE is a disease in which a person's normal immunity is upset. The body produces an excess of blood proteins called antibodies and these antibodies may cause problems in any organ of the body.

These antibodies may end up, for example, in the skin causing a variety of skin rashes or deposit in the kidney, brain, lung and joints causing injury.

Discoid Lupus Erythematous (DLE)

DLE is similar to SLE except it only affects the skin and is characterised by a scaling, red rash.

Malaria (treatment and control of symptoms)

Malaria is an infectious disease caused by the presence of parasites in red blood cells.

The disease is characterised by chills, fever and sweats.

In malaria, Hydroxychloroquine Winthrop destroys the harmful parasite which causes the illness.

Your doctor may have prescribed this medicine for another reason. Ask your doctor if you have any questions about why Hydroxychloroquine Winthrop has been prescribed for you.

Hydroxychloroquine Winthrop is not addictive. This medicine is available only with a doctor's prescription.

Before you take Hydroxychloroquine Winthrop

When you must not take Hydroxychloroquine Winthrop

Do not take Hydroxychloroquine Winthrop if you have ever had an allergic reaction to hydroxychloroquine, chloroquine, or related products or any of the ingredients listed under "Product Description".

If you are uncertain whether you have had an allergic reaction to a related product ask your doctor or pharmacist.

The symptoms of an allergic reaction may include an asthma attack, facial swelling, skin rash or hay fever.

Ask your doctor about the risks and benefits of taking Hydroxychloroquine Winthrop while you are pregnant.

When Hydroxychloroquine Winthrop is taken for long periods of time, there is an increased risk to the unborn child. It may cause problems with brain function, hearing, balance and vision.

Ask your doctor about the risks and benefits of taking Hydroxychloroquine Winthrop while you are breastfeeding.

Do not take Hydroxychloroquine Winthrop if you have previously experienced changes in your eyesight when taking medicines for rheumatoid arthritis or malaria.

Hydroxychloroquine Winthrop should not be used in children under 6 years.

Hydroxychloroquine Winthrop should not be used in children over 6 years for long periods.

Do not take Hydroxychloroquine Winthrop after the expiry date printed on the bottle.

It may have no effect at all, or worse, an entirely unexpected effect if you take it after the expiry date.

Do not take Hydroxychloroquine Winthrop if the bottle is damaged or shows signs of tampering.

Do not take Hydroxychloroquine Winthrop to treat any other complaint unless your doctor says it is safe. Do not give this medicine to anyone else.

Before you start to take Hydroxychloroquine Winthrop

You must tell your doctor if:

- You are allergic to quinine.
- You have allergies to any ingredients listed under "Product Description" at the end of this leaflet.
- You have any pre-existing eye disorders.
-
- You have experienced low blood sugar levels (hypoglycaemia – a "hypo"). Hydroxychloroquine Winthrop may increase the risk of you having a hypo.
- You have or have had any of these medical conditions:
  - Chloroquine-resistant malaria
  - Liver or kidney problems
  - Diabetes
  - Stomach, brain or blood disorders
  - Disease of the heart muscle
  - Skin diseases, in particular psoriasis which is a kind of itchy rash.
  - Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency which is a lack of a chemical substance which causes the breakdown of sugar in the body.
  - Porphyria, which is a rare disease of blood pigments.

If you have not told your doctor about any of these things, tell him/her before you take any Hydroxychloroquine Winthrop .

Taking Hydroxychloroquine Winthrop with other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines may interfere with Hydroxychloroquine Winthrop . These include:

- Any medicine to treat depression
- Digoxin - a medicine used to treat heart disease
- Medicines to treat diabetes
- Medicines used to suppress the immune system such as cyclosporin
- Antiarrythmic drugs such as amiodarone
- Other antimalarial drugs
- Medicines to treat epilepsy

These medicines may be affected by Hydroxychloroquine Winthrop or affect the way Hydroxychloroquine Winthrop works.

Your doctor or pharmacist can tell you what to do if you are taking any of these medicines.

How to take Hydroxychloroquine Winthrop

Swallow tablets whole with a little water or other liquid.

It is best to take Hydroxychloroquine Winthrop at meal times.

The dosage will depend on why you are being treated with Hydroxychloroquine Winthrop .

The usual doses are:

Rheumatoid arthritis

Adults

2-3 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

SLE and DLE

Adults

2-4 tablets daily. Your doctor may later reduce this to 1-2 tablets daily.

Control of Malaria Symptoms

Adults

2 tablets once a week. The tablets should be taken on exactly the same day of each week.

For example, if your first dose is taken on a Monday, then each weekly dose should be taken on a Monday.

Treatment of malaria

Adults

The starting dose is 4 tablets. Take another 2 tablets six to eight hours later and two further tablets on each of the next 2 days.

Always follow the instructions given to you by your doctor.

Dosages for children are calculated according to the child's body weight.

Your doctor will work out the correct dose for you.

Hydroxychloroquine Winthrop should not be used in children for long periods.

Your doctor may ask you to take a different dose. You should follow the instructions on the label.

If you are unsure what dose to take ask your pharmacist or doctor.

If you forget to take Hydroxychloroquine Winthrop

If you are being given Hydroxychloroquine Winthrop for rheumatoid arthritis, SLE or DLE, do not take a double dose to make up for the dose missed. Just continue with the appropriate dose on the next day.

If you are being given Hydroxychloroquine Winthrop for suppression or treatment of malaria, you should take your tablets as soon as you remember, and go back to taking it as you would normally.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much Hydroxychloroquine Winthrop (Overdose)

Immediately telephone your doctor, or the Poisons Information Centre (in Australia telephone 13 11 26 and in New Zealand telephone 0800 POISON or 0800 764766), or go to Accident and Emergency at your nearest hospital, if you think that you or anyone else may have taken too much Hydroxychloroquine Winthrop .

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too many tablets you may experience headaches, drowsiness, visual disturbances or fits.

These symptoms may occur within 30 minutes of overdose.

While you are taking Hydroxychloroquine Winthrop

If you are about to start taking any new medicines, tell your doctor and pharmacist that you are taking Hydroxychloroquine Winthrop.

Tell all doctors, dentists and pharmacists who are treating you that you are taking Hydroxychloroquine Winthrop.

Tell your doctor if you experience any of the following symptoms including; weakness, trembling or shaking, sweating, light-headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers. These symptoms may be associated with hypoglycaemia.

If you experience any of the symptoms of hypoglycaemia, you need to raise your blood glucose urgently. You can do this by taking one of the following:

- 5-7 jelly beans
- 3 teaspoons of sugar or honey
- 1/2 can of ordinary (non-diet) soft drink
- 2-3 concentrated glucose tablets
- unless you are within 10 to 15 minutes of your next meal or snack, follow up with extra carbohydrates e.g. plain biscuits, fruit or milk - when over the initial symptoms. Taking this extra carbohydrate will prevent a second drop in your blood glucose level.

Make sure you, your friends, family and work colleagues can recognise the symptoms of hypoglycaemia and know how to treat them.

Your doctor will need to perform the following tests during treatment with Hydroxychloroquine Winthrop:

Eye Tests

Your doctor will need to perform some eye tests every few months to check that your eyesight is not changing.

In extremely rare cases, Hydroxychloroquine Winthrop has been associated with blindness. This can be avoided by having regular eye tests.

It is recommended you wear sunglasses when out in the sun.

Blood Tests

Your doctor will need to perform occasional blood tests to check for any blood reactions.

Driving/Operating Machinery

Be careful driving or operating machinery until you know how Hydroxychloroquine Winthrop affects you.

Hydroxychloroquine Winthrop may cause problems with the eyesight of some people. Make sure you know how you react to Hydroxychloroquine Winthrop before you drive a car, operate machinery, or do anything else that could be dangerous with blurred vision.

Side Effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while taking Hydroxychloroquine Winthrop .

Hydroxychloroquine Winthrop helps most people with rheumatoid arthritis, SLE, DLE, treatment of malaria and the control of malaria

symptoms, but it may have unwanted side effects in a few people.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions.

Tell your doctor if you notice any of the following and they worry you:

Less serious side effects

Stomach problems such as:

- Nausea
- Vomiting
- Diarrhoea
- Abdominal cramps

Other problems such as:

- Loss of appetite
- Muscle weakness
- Dizziness
- Ringing in the ears
- Headache
- Nervousness
- Skin rash and itching
- Hair loss

If you already have psoriasis, you are more likely to experience skin reactions than other people when taking Hydroxychloroquine Winthrop .

More serious side effects

Tell your doctor if you notice any of the following:

- Visual disturbances
- Any hearing loss
- Suicidal behaviour
- Frequent fevers, severe chills, bruising, sore throat or mouth ulcers (these may be signs of blood reactions)
- More severe symptoms of hypoglycaemia, including:
  - disorientation
  - seizures, fits or convulsions
  - loss of consciousness

These are serious side effects. You may need urgent medical attention.

Serious side effects are rare.

Tell your doctor if you notice anything else that is making you feel unwell.

Some people may get other side effects while taking Hydroxychloroquine Winthrop .

After taking Hydroxychloroquine Winthrop

Storage

Keep your tablets in the bottle until it is time to take them.

If you take the tablets out of the bottle they will not keep well.

Keep it in a cool dry place where the temperature stays below 25°C.

Heat and dampness can destroy some medicines. Do not leave Hydroxychloroquine Winthrop in the car on hot days.

Do not store Hydroxychloroquine Winthrop or any other medicine in the bathroom or near a sink.

Keep Hydroxychloroquine Winthrop where young children cannot reach it.

Children are particularly sensitive to the unwanted effects of Hydroxychloroquine Winthrop .

A locked cupboard at least one and a half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking the tablets, ask your pharmacist what to do with any tablets that are left over.

Product Description

What Hydroxychloroquine Winthrop looks like

Hydroxychloroquine Winthrop comes as white to off-white peanut shaped tablets marked " HCQ 200 " with black ink. A bottle contains 100 tablets.

Ingredients

Active Ingredient

Each Hydroxychloroquine Winthrop tablet contains 200mg hydroxychloroquine sulfate.

Other ingredients

- Calcium Hydrogen Phosphate
- Starch-Maize
- Magnesium Stearate
- Water-Purified
- Hypromellose
- Macrogol 400
- Titanium dioxide
- Polysorbate 80
- Carnauba Wax
- Black Ink

Australian Registration Number

AUST R 52267

Supplier

Hydroxychloroquine Winthrop is supplied in Australia by:

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

Hydroxychloroquine Winthrop is supplied in New Zealand by:

sanofi-aventis new zealand limited
56 Cawley St
Ellerslie, Auckland, New Zealand
Phone: (09) 580 1810

This leaflet was prepared in April 2014.

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