

# DATA SHEET

## 1 PRODUCT NAME

PLAQUENIL 200mg Tablet, film coated

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydroxychloroquine sulfate 200mg equivalent to 155mg hydroxychloroquine.

For full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Film coated tablet.

White to off-white peanut shaped tablets, marked "Plaquenil" in black ink on one face of the tablet.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Acute and chronic rheumatoid arthritis; mild systemic and discoid lupus erythematosus; the suppression and treatment of malaria.

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If a relapse occurs after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.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

## **4.3 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.

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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.

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 a sensitivity to quinine, and in glucose-6-phosphate dehydrogenase deficiency.

#### **Chronic Cardiac Toxicity**

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.

#### **Hypoglycaemia**

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 section 4.8)

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

Before starting a long term treatment, both eyes should be examined (for visual acuity, central visual field and colour vision, and fundoscopy. Wherever possible, optical coherence tomography (OCT) is recommended). Then the examination should be repeated at least annually.

Ophthalmological testing should be more frequent and adapted to the patient, 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 5 years.

The examination should include slit-lamp microscopy (for corneal opacities) and fundus and visual field studies.

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.

### **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.

### **Other Monitoring On Long Term Treatments**

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

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.

### **QT Interval prolongation**

Hydroxychloroquine has the potential to prolong the QTc interval in patients with specific risk factors. Hydroxychloroquine should be used with caution in patients with congenital or documented acquired QT prolongation and/or known risk factors for prolongation of the QT interval such as:

- advanced age,
- renal or hepatic disease,
- uncorrected hypokalaemia and/or hypomagnesaemia
- cardiac disease, e.g., heart failure, myocardial infarction
- proarrhythmic conditions, e.g., bradycardia (< 50 bpm)
- a history of ventricular dysrhythmias
- an underlying genetic predisposition, or
- during concomitant administration with QT interval prolonging agents (see Section 4.5) as this may lead to an increased risk for ventricular arrhythmias.

The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded (see Section 4.5 and Section 4.8).

### **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.

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.

Suicidal behaviour and psychiatric disorders have been reported in some patients treated with hydroxychloroquine.

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

Extrapyramidal disorders may occur with hydroxychloroquine.

### **Potential Carcinogenic Risk**

Experimental data showed a potential risk of inducing gene mutations. Animal carcinogenicity data is only available for one species for the parent drug chloroquine and this study was negative. In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving long term treatment.

## **4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

### **Pharmacodynamic Interactions**

Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia:  
Hydroxychloroquine should be used with caution in patients receiving drugs known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia (see Section 4.4 and Section 4.9).  
Halofantrine should not be administered with hydroxychloroquine.

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

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.

There is a theoretical risk of inhibition of intra-cellular  $\alpha$ -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

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

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

Hydroxychloroquine sulphate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

## **Pharmacokinetic Interactions**

### **Effects of other medicinal products on hydroxychloroquine:**

#### ***Antacids and kaolin***

Concomitant administration with magnesium-containing antacids or kaolin may result in reduced absorption of chloroquine. Per extrapolation, hydroxychloroquine should therefore be administered at least two hours apart from antacids or kaolin.

#### ***CYP inhibitors or inducers***

Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for hydroxychloroquine. Caution is advised (e.g. monitoring for adverse reactions) when CYP2C8 and CYP3A4 strong or moderate inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice) are concomitantly administered.

Lack of efficacy of hydroxychloroquine was reported when rifampicin, a CYP2C8 and CYP3A4 strong inducer, was concomitantly administered. Caution is advised (e.g. monitoring for efficacy) when CYP2C8 and CYP3A4 strong inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) are concomitantly administered.

### **Effects of hydroxychloroquine on other medicinal products:**

#### ***P-glycoprotein substrates***

The inhibitory potential of hydroxychloroquine on P-gp substrates has not been evaluated. In vitro observations show that all other aminoquinolines tested inhibit P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered.

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



Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were coadministered. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, ciclosporin, dabigatran) are concomitantly administered.

### ***Praziquantel***

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.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Fertility**

There are no animal data on hydroxychloroquine action on fertility.

Only limited reproductive toxicity data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the 2 products.

A study in male rats showed a decrease in testosterone levels, weight of testes, epididymis, seminal vesicles and prostate after 30 days of oral treatment at 5 mg/day of chloroquine. In another rat study with chloroquine, the male fertility rate was decreased after 14 days of intraperitoneal treatment at 10 mg/kg/day.

There are no data in humans.

### **Pregnancy**

#### Category D

Hydroxychloroquine crosses the placenta. It should be noted 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. Literature review of observational data and meta-analyses, on the use of hydroxychloroquine in women with autoimmune disease during pregnancy excluded a large risk of congenital malformations (RR>3). However, the statistical power to detect modest risks was limited and various limitations of observational data do not allow robust exclusion of causality.

Due to lack of studies, no conclusions can be made from the epidemiologic literature about paternal exposure to Hydroxychloroquine affecting fertility or birth outcomes.

In animal studies on chloroquine, embryo-fetal development toxicity was shown at very high, supratherapeutic doses (ranging from 250 to 1500 mg/kg bodyweight).

Hydroxychloroquine should be avoided in pregnancy except when, in the judgement of the physician, the individual 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 fetus is outweighed by the benefits to the mother and fetus.

#### **Lactation:**

Hydroxychloroquine is excreted in breast milk (less than 2% of the maternal dose after bodyweight correction).

Breastfeeding is possible in case of curative treatment of malaria. Although hydroxychloroquine is excreted in breast milk, the amount is insufficient to confer any protection against malaria to the infant. Separate chemoprophylaxis for the infant is required.

There are very limited data on the safety in the breastfed infant during hydroxychloroquine long-term treatment; the prescriber should assess the potential risks and benefits of use during breastfeeding, according to indication and duration of treatment.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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.

#### **4.8 UNDESIRABLE EFFECTS**

*Note* *very common*  $\geq 1/10$  ( $\geq 10\%$ )

*common*  $\geq 1/100$  and  $< 1/10$  ( $\geq 1\%$  and  $< 10\%$ )

*uncommon*  $\geq 1/1000$  and  $< 1/100$  ( $\geq 0.1\%$  and  $< 1.0\%$ )

*rare*  $\geq 1/10,000$  and  $< 1/1000$  ( $\geq 0.01\%$  and  $< 0.1\%$ )

*very rare*  $< 1/10,000$  ( $< 0.01\%$ )

*not known* *frequency cannot be estimated from available data*

#### **Blood and Lymphatic System Disorders**

*Not known:* bone marrow depression, anaemia, aplastic anaemia, leucopenia, thrombocytopenia, agranulocytosis

## **Immune System Disorders**

*Not known* urticaria, angioedema, bronchospasm

## **Metabolism and Nutritional Disorders**

*Common:* anorexia

*Not known* hypoglycaemia

Hydroxychloroquine may exacerbate porphyria

## **Psychiatric Disorders**

*Common* affect lability

*Uncommon:* nervousness

*Very rare:* nightmares

*Not known* psychosis, suicidal behaviour, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders

## **Nervous System Disorders**

*Common:* headache

*Uncommon:* dizziness, nerve deafness

*Very rare:* nystagmus, ataxia

*Not known:* convulsions, extrapyramidal disorders such as dystonia, dyskinesia, tremor

## **Eye Disorders**

*Common:* blurring of vision

*Uncommon:* corneal changes, retinal changes, retinopathy with changes in pigmentation and visual field defects. 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.

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.

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

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.

See section 4.4 for information on eye examinations.

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.

### **Ear and Labyrinth Disorders**

*Uncommon:* vertigo, tinnitus

*Not known:* hearing loss

### **Cardiac Disorders**

*Not known:* cardiomyopathy which may result in cardiac failure, and in some cases a fatal outcome (see section 4.4)

QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia) (See Section 4.4 and 4.5).

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

### **Gastrointestinal Disorders**

*Very common:* abdominal pain, nausea

*Common:* diarrhoea, vomiting

### **Hepatobiliary Disorders**

*Uncommon:* abnormal liver function tests

*Not known:* fulminant hepatitis

### **Skin and Subcutaneous Tissue Disorders**

*Common:* skin rashes, pruritus

*Uncommon:* pigmentary changes, bleaching of hair, alopecia

*Rare:* exacerbation or precipitation of porphyria and attacks of psoriasis

*Not known:* bullous eruptions such as acute generalised exanthematous pustulosis (AGEP), exfoliative dermatitis and erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), toxic epidermal necrolysis, photosensitivity

### **Musculoskeletal and Connective Tissue Disorders**

*Uncommon:* sensori 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**

*Very rare:* weight loss, lassitude

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at <https://nzphvc.otago.ac.nz/reporting/>

## 4.9 OVERDOSE

### 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.

The ECG may reveal rhythm and conduction disorders including, QT prolongation, torsade de pointe, ventricular tachycardia, ventricular fibrillation, width-increased QRS complex, bradyarrhythmias (including bradycardia), nodal rhythm, atrioventricular block, followed by sudden potentially fatal respiratory and 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. 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.

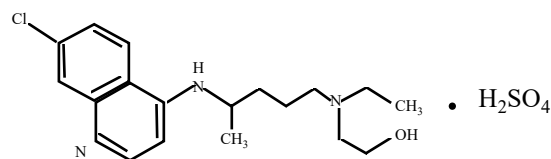
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimalarials, ATC code: P01BA02

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 No. 747-36-4 (hydroxychloroquine sulfate), CAS No. 118-42-3 (hydroxychloroquine).

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*.

## 5.2 PHARMACOKINETIC PROPERTIES

Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine. Following oral administration, hydroxychloroquine is rapidly and almost completely absorbed. In one study, mean peak plasma hydroxychloroquine concentrations following a single dose of 400mg in healthy subjects ranged from 53-208ng/mL with a mean of 105ng/mL. The mean time to peak plasma concentration was 1.83 hours. The mean plasma elimination half-life varied, depending on the post-administration period, as follows: 5.9 hours (at  $C_{max}$  -10 hours), 26.1 hours (at 10-48 hours) and 299 hours (at 48-504 hours). The parent compound and metabolites are widely distributed in the body and elimination is mainly via the urine, where 3% of the administered dose was recovered over 24 hours in one study.

### Absorption

Following oral administration, peak blood concentration is achieved in approximately 4 hours. Absolute oral bioavailability is 79%.

## **Distribution**

Hydroxychloroquine has a large volume of distribution due to extensive tissue accumulation (5500 L in blood, 44 000 L in plasma), and has been shown to accumulate in blood cells, with a blood to plasma ratio of 7.2. Approximately 50% of hydroxychloroquine is bound to plasma proteins.

## **Metabolism**

Hydroxychloroquine is mainly metabolized to N-desethylhydroxychloroquine, and two other metabolites in common with chloroquine, desethylchloroquine and bidesethylchloroquine. It can be extrapolated from chloroquine, that hydroxychloroquine could be metabolized *in vitro* by the same CYPs as for chloroquine, i.e. CYP2C8 and CYP3A, and to a lesser extent by CYP2D6.

## **Elimination**

Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 to 60 days. Approximately 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

Based on the standard genotoxicity studies conducted, hydroxychloroquine is not considered to present a genotoxic risk to humans.

Hydroxychloroquine is not mutagenic in the bacterial reverse mutation (Ames) test.

It showed no clastogenicity or aneugenicity in the *in vivo* micronucleus test in rats following oral administration. Hydroxychloroquine was weakly positive in human lymphocyte micronucleus assay *in vitro* in the absence of metabolic activation, but was negative in the presence of metabolic activation.

### **Carcinogenicity**

No carcinogenicity studies are available on hydroxychloroquine. A dietary carcinogenicity study in rats with the parent drug chloroquine was negative. No other carcinogenicity study was conducted in mice or other species. In the absence of sufficient human and animal data an increased risk of cancer in patients receiving long term treatment cannot be ruled out.



## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

*Tablet core:*

Calcium hydrogen phosphate dihydrate  
Maize starch  
Purified water  
Magnesium stearate

*Film coating:*

Hypromellose  
Macrogol 400  
Titanium dioxide  
Polysorbate 80  
Carnauba wax  
iron oxide black (Tekprint SB-9014SD)  
propylene glycol  
isopropyl alcohol  
ethanol  
dimeticone  
butan-1-ol  
Purified water

### **6.2 INCOMPATIBILITIES**

No incompatibilities are known.

### **6.3 SHELF LIFE**

36 months.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Plaquenil tablets should be stored below 25° C.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

Plaquenil is supplied as 100 tablets in a plastic HDPE bottle with a child resistant closure.

## **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

None.

## **7 MEDICINE SCHEDULE**

Prescription Medicine

## **8 SPONSOR**

sanofi-aventis new zealand limited  
56 Cawley Street, Ellerslie,  
Auckland New Zealand

Toll Free Number (medical information): 0800 283 684

Email: [medinfo.australia@sanofi.com](mailto:medinfo.australia@sanofi.com)

## **9 DATE OF FIRST APPROVAL**

31 December 1969

## **10 DATE OF REVISION OF THE TEXT**

21 January 2022

## **SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
4.5	Editorial changes
4.6	Update to text under Fertility and Pregnancy subsections
5.3	Inclusion of text relating to genotoxicity and carcinogenicity