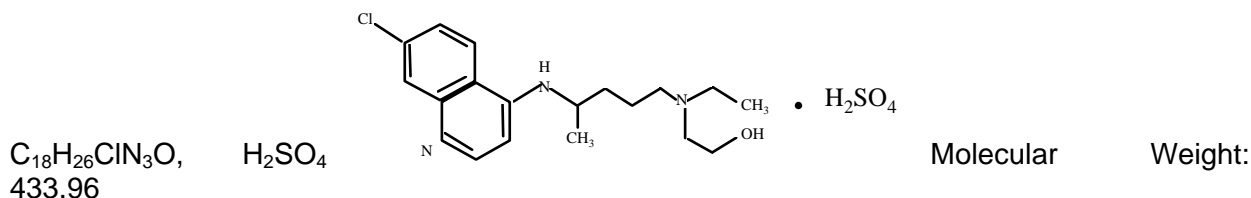


# PLAQUENIL DATA SHEET

## COMPOSITION

Film coated tablets containing hydroxychloroquine sulfate 200 mg (equivalent to 155 mg base). CAS No. 747-36-4 (hydroxychloroquine sulphate), CAS No. 118-42-3 (hydroxychloroquine). Hydroxychloroquine sulfate is designated chemically as 2-[N-(4-(7-Chloro-4-quinolylamino)pentyl)-N-ethylamino]ethanol sulfate, and has the following chemical structure:



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.

## ACTIONS

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.

## PHARMACOLOGY

### 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

Acute and chronic 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.

## WARNINGS

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.

## PRECAUTIONS

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.

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 overdose 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, 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.

## **Cardiac Conduction Defects**

Cases of QT interval prolongation, torsades de pointes and sudden cardiac death have been observed with hydroxychloroquine use. Although the majority of cases occurred in the overdose setting, an association with therapeutic use cannot be ruled out. Hydroxychloroquine should be used cautiously in patients with other risk factors for QT prolongation including advanced age, renal or hepatic disease, hypokalaemia or severe hypomagnesaemia, structural heart disease, bradycardia, an underlying genetic predisposition, or in patients using other potential QT prolonging medicines.

## **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.

## **Use In Pregnancy**

### Category D

The use of this drug in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus. Prophylaxis in high-risk situations is also justified. 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.

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.

## DRUG INTERACTIONS

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.

## ADVERSE REACTIONS

- Ophthalmological

*Rare:* Corneal Changes

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.

*Rare:* Retinal Changes

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 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*

Urticaria, angioedema and bronchospasm have been reported.

- Blood Disorders

*Rare:* bone marrow depression, anaemia, aplastic anaemia, leucopenia, thrombocytopenia

*Very rare:* agranulocytosis

Hydroxychloroquine may exacerbate porphyria

- Central Nervous System
  - Uncommon:* vertigo, tinnitus, headache, nerve deafness
  - Rare:* convulsions, neuromyopathy
  - Very rare:* nervousness, emotional lability, psychosis, nightmares, nystagmus, ataxia, dizziness
- Neuromuscular
  - Uncommon:* 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) Associated mild sensory changes and abnormal nerve conduction may be observed.
  - Very rare:* extraocular muscle palsies
- Gastrointestinal
  - Common:* nausea, diarrhoea, abdominal pain
  - Rare:* anorexia, vomiting
- Liver Disorders
  - Rare:* abnormal liver function tests
  - Very rare:* fulminant hepatitis
- Cardiovascular Disorders
  - Rare:* cardiomyopathy
- Dermatological
  - Common:* skin rashes, alopecia
  - Uncommon:* pigmentary changes
  - Very rare:* bleaching of hair, acute generalised exanthematous pustolosis (AGEP), exfoliative dermatitis and erythema multiforme, Stevens-Johnson syndrome, photosensitivity, pruritus
- Miscellaneous
  - Rare:* exacerbation or precipitation of porphyria and attacks of psoriasis
  - Very rare:* weight loss, lassitude

Note	<i>very common</i>	≥ 1/10 (≥ 10%)
	<i>common</i>	≥ 1/100 and < 1/10 (≥1% and <10%)
	<i>uncommon</i>	≥ 1/1000 and < 1/100 (≥0.1% and <1.0%)
	<i>rare</i>	≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	<i>very rare</i>	< 1/10,000 (< 0.01%)

## 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, 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 QT prolongation and progressive bradycardia leading to ventricular fibrillation and/or cardiac arrest.

### **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.

## **MEDICINE CLASSIFICATION**

Prescription Medicine

## **PRESENTATION**

White to off-white peanut shaped tablets, marked "Plaquenil" in black ink on one face of the tablet. 100s.

**STORAGE**

Plaquenil tablets should be stored below 25° C.

**NAME AND ADDRESS**

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**DATE OF PREPARATION**

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