

PRODUCT INFORMATION

1. NAME OF THE MEDICINE

PLAQUENIL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film coated tablets containing hydroxychloroquine sulfate 200 mg (equivalent to 155 mg base).

~~Excipients with known effect: none.~~

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

Plaquenil is indicated for the suppressive treatment and treatment of acute attacks of malaria due to *Plasmodium vivax*, *p. malaria*, *p. ovale* and susceptible strains of *p. falciparum*.

It is also indicated for the treatment of discoid and systemic lupus erythematosus and rheumatoid arthritis

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If a relapse occurs after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.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

Corticosteroids and salicylates may be used in conjunction with this compound, and they 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.

Lupus Erythematosus

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~~ affects the complete cure of the infection, unless due to a resistant strain of *P.falciparum*.

Malaria prevention

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.

4.3 CONTRAINDICATIONS

Plaquenil is contraindicated in:

- patients with pre-existing maculopathy of the eye
- ~~H~~ypersensitivity to the active substance or to any of the excipients listed in section 2.
- ~~in the presence of retinal or visual field changes attributable~~ patients with known hypersensitivity to any 4-aminoquinoline compound
- 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.

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 hypoglycemia 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.

QT interval prolongation

Hydroxychloroquine prolongs the QTc interval and should not be used 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 4.5 Interactions with other medicines and other forms of interactions and Section 4.9 Overdose).

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:

- cardiac disease, e.g., heart failure, myocardial infarction
- proarrhythmic conditions, e.g., bradycardia (< 50 bpm)
- a history of ventricular dysrhythmias
- uncorrected hypokalaemia and/or hypomagnesaemia

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 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (Undesirable effects)).

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-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 Adverse effects (Undesirable effects)).

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

Before starting treatment with hydroxychloroquine all patients should have a careful complete examination of both eyes which includes slit-lamp microscopy for corneal opacities, fundoscopy, visual acuity, central visual field and colour vision. 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. 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

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 reaction

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.

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

Extrapyramidal disorders may occur with hydroxychloroquine.

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.

Use in hepatic impairment

Observed caution in patients with hepatic disease, as well as in those taking medicines known to affect the organ. A reduction in dosage may be necessary.

Use in renal impairment

Observed caution in patients with renal disease, as well as in those taking medicines known to affect the organ. A reduction in dosage may be necessary.

Use in the elderly

See Section 4.4 Special warnings and precautions for use – Ophthalmological.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic Interactions

Drugs are known to prolong QT interval / with potential to induce cardiac arrhythmia:
Hydroxychloroquine should not be used 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 4.5 Special precautions and warnings for use and Section 4.9 Overdose). Halofantrine should not be administered with hydroxychloroquine.

Antidiabetic drugs

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

Antimalarials

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.

Antiepileptic drugs

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

Others

There is a theoretical risk of inhibition of intra-cellular α -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.

~~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.~~

~~Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia: Hydroxychloroquine should not be used 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 Special precautions and warnings for use and Section 4.9 Overdose). Halofantrine should not be administered with hydroxychloroquine.~~

~~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.~~

Effects of other medicinal products on hydroxychloroquine:

Antacids

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-gp 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.

~~There is a theoretical risk of inhibition of intra-cellular α -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.~~

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no animal data on hydroxychloroquine action on fertility. ~~Animal studies showed an impairment of male fertility for chloroquine, a parent drug (see Section 5.3). 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 with chloroquine at 5 mg/day. 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.

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. 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.

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-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

Hydroxychloroquine is excreted in breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinones. In one study, the daily HCQ exposures to infant from breast milk were estimated to be less than 2% of the maternal dose (after bodyweight correction).

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 long-term hydroxychloroquine 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 ADVERSE EFFECTS

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

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

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

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

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

Very rare: agranulocytosis

Immune System Disorders

Not known: urticaria, angioedema, bronchospasm.

Metabolism and nutrition disorders

Common: anorexia

Not known: hypoglycemia

Hydroxychloroquine may exacerbate porphyria

Psychiatric Disorders

Common: affect lability

Very rare: psychosis, suicidal behavior, nightmares

Nervous System Disorders

Common: headache

Uncommon: dizziness nerve deafness, nervousness,

Rare: convulsions, neuromyopathy

Very rare: nystagmus, ataxia

Not known: 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 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.

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.

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

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.

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.

Before starting treatment with hydroxychloroquine all patients should have a carefully complete examination, of both eyes which includes slit lamp microscopy for corneal changes, fundoscopy, visual acuity, central visual field and colour vision repeated at six-month intervals during therapy. (see Section 4.4 Special warnings and precautions for use- Ophthalmological).

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

Rare: cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see Section 4.4 Special warnings and precautions for use).

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

Not known: QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia) (See section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

Gastrointestinal Disorders

Very common: abdominal pain, nausea

Common: diarrhoea, vomiting.

Hepatobiliary Disorders

Uncommon: abnormal liver function tests

Very rare: fulminant hepatitis

Skin and Subcutaneous Tissue Disorders

Common: skin rashes, alopecia, pruritus

Uncommon: pigmentary changes, bleaching of hair

Very rare: bullous eruptions such as 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.

Musculoskeletal and Connective Tissue Disorders

Uncommon: sensorimotor 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

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

4.9 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. 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.

5. PHARMACOLOGY PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Pharmacotherapeutic group: Antimalarials, ATC code: P01BA

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~~ affects the complete cure of the infection, unless due to a resistant strain of *P.falciparum*.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Reproductive toxicity

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

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

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 with chloroquine at 5 mg/day. In another rat study with chloroquine the male fertility rate was decreased after 14 days of intraperitoneal treatment at 10 mg/kg/day.

Genotoxicity

There are limited data on hydroxychloroquine genotoxicity. Chloroquine is reported in the literature to elicit both gene mutations and chromosomal/DNA breaks in some in vitro systems but not others and in in vivo studies using rodents when dosed via the intraperitoneal route. Chromosomal effects were not observed in vivo when chloroquine was administered orally.

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 PARTICULAR

6.1 LIST OF EXCIPIENTS

Starch, Dibasic Calcium Phosphate, and Magnesium Stearate. The film coating contains: Opardy White (YS-1-7443), Polyethylene Glycol (PEG 4000), Carnauba Wax, Tekprint SB-9014SD Black Ink and Film-coating Water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf life after opening: until the end of the registered shelf life.
The expiry date can be found on the packaging.

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 Is an HDPE bottle

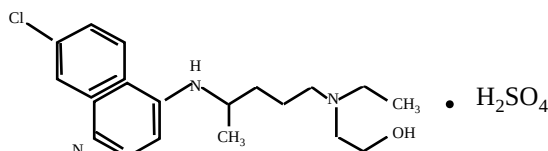
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

6.7 PHYSICOCHEMICAL PROPERTIES

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 NUMBER

747-36-4 (hydroxychloroquine sulphate)

118-42-3 (hydroxychloroquine).

7. MANUFACTURER

Sanofi Winthrop Industrie, France.

8. LICENSE HOLDER

Sanofi-Aventis Israel LTD.

10 Beni Gaon, POB 8090, Netanya, Israel.

Revised in January 2021