

PRODUCT MONOGRAPH

PrMylan-Hydroxychloroquine

Hydroxychloroquine Sulfate Tablets

200 mg

USP

Anti-Inflammatory - Antimalarial

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, Ontario
Canada, M8Z 2S6

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PrMYLAN-HYDROXYCHLOROQUINE

Hydroxychloroquine Sulfate Tablet

200 mg

USP

THERAPEUTIC CLASSIFICATION

Anti-inflammatory - Antimalarial

ACTIONS AND CLINICAL PHARMACOLOGY

Mylan-Hydroxychloroquine (Hydroxychloroquine sulfate) belongs to the 4-aminoquinoline class. Mylan-Hydroxychloroquine has been beneficial for patients with rheumatoid arthritis and lupus erythematosus, especially chronic discoid lupus. The exact mode of action in controlling these diseases is unknown. The action of this compound against malarial parasites is similar to that of chloroquine phosphate.

INDICATIONS AND CLINICAL USE

MYLAN-HYDROXYCHLOROQUINE (hydroxychloroquine sulfate) is indicated for the treatment of rheumatoid arthritis, and discoid and systemic lupus erythematosus, in patients who have not responded satisfactorily to drugs with less potential for serious side effects.

It is also indicated for the suppressive treatment and treatment of acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is not active against the exo-erythrocytic forms of *P. vivax*, *P. malariae* and *P. ovale* and therefore will neither prevent infection due to these organisms when given prophylactically, nor prevent relapse of infection due to these organisms. 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*.

CONTRAINDICATIONS

- pre-existing retinopathy of the eye
- patients with known hypersensitivity to 4-aminoquinoline compounds
- use in children below 6 years of age (200 mg tablets not adapted for weight <35 kg) (see WARNINGS AND PRECAUTIONS, Special Populations – Pediatric Use).

WARNINGS AND PRECAUTIONS

General:

Observe caution in patients with gastrointestinal or neurological disorders, in those with sensitivity to quinine, and in porphyria.

Effects on Ability to Drive and Use Machinery:

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

Malaria:

Hydroxychloroquine sulfate tablets is not effective against chloroquine-resistant strains of *P. falciparum* and is not active against the exo-erythrocytic forms of *P. vivax*, *P. ovale* and *P. malarias* and therefore will neither prevent infection due to these organisms when given prophylactically, nor prevent relapse of infection due to these organisms.

Carcinogenesis and Mutagenesis:

Non-clinical studies showed a potential risk of chloroquine inducing gene mutations. Long term studies in animals have not been conducted to evaluate the carcinogenic potential (see TOXICOLOGY). In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving-long term treatment.

Cardiovascular:

Cases of cardiomyopathy resulting in cardiac failure, in some cases with a fatal outcome, have been reported in patients treated with Mylan-Hydrochloroquine. Mylan-Hydrochloroquine should be discontinued if signs and symptoms of cardiomyopathy develop. Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed (see ADVERSE REACTIONS and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Mylan-Hydroxychloroquine may induce cardiac arrhythmia (see DRUG INTERACTIONS and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Hydroxychloroquine sulfate prolongs the QT interval. Ventricular arrhythmias and torsades de pointes have been reported in patients taking hydroxychloroquine sulfate (see OVERDOSAGE). Therefore, Mylan-Hydrochloroquine should not be administered with other drugs that have the potential to prolong the QT interval. Mylan-Hydrochloroquine should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, and risk factors for drug-induced QT/QTc prolongation (see DRUG INTERACTIONS, ADVERSE REACTIONS, and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Endocrine and Metabolism:

Mylan-Hydroxychloroquine has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic

medications. Patients treated with Mylan-Hydroxychloroquine should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with Mylan-Hydroxychloroquine should have their blood glucose level checked and the need for Mylan-Hydroxychloroquine treatment reviewed as necessary. In cases of severe hypoglycemia, Mylan-Hydroxychloroquine should be discontinued and alternative therapy considered. If patients use Mylan-Hydroxychloroquine concomitantly with antidiabetic drugs, a decrease in doses of insulin or antidiabetic drugs may be required as Mylan-Hydroxychloroquine may enhance the effects of hypoglycemic treatment (see DRUG INTERACTIONS and ADVERSE REACTIONS).

Hematologic:

Periodic blood counts should be obtained in patients requiring prolonged therapy due to the risk of bone marrow depression (see ADVERSE REACTIONS). If any severe blood disorder appears that is not attributable to the disease under treatment, the drug should be discontinued.

Observe caution in patients with blood disorders or glucose-6-phosphate dehydrogenase deficiency.

Musculoskeletal:

All patients on long term therapy with this preparation should be questioned and examined periodically, including the examination of skeletal muscle function and tendon reflexes, testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug (see ADVERSE REACTIONS).

Neurologic:

Extrapyramidal reactions have been reported in patients taking Mylan-Hydroxychloroquine (see ADVERSE REACTIONS). Symptoms may persist in some patients after discontinuation of therapy.

Ophthalmologic:

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Before starting a long term treatment, both eyes should be examined by careful ophthalmoscopy for visual acuity, central visual field and color vision, and fundoscopy. Then, the examination should be repeated at least annually.

Retinal toxicity is largely dose-related. The risk of retinal damages is small with daily doses of up to 6.5 mg/kg ideal (lean) body weight. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity. Significant risk factors for toxic retinopathy reported during long-term (≥ 5 years) treatment with hydroxychloroquine include daily doses greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, subnormal glomerular filtration rate, durations of use longer than five years, and concurrent treatment with tamoxifen citrate. Concomitant use of Mylan-Hydroxychloroquine with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

Careful ophthalmologic examination should be more frequent and adapted to the patient, in the following situations:

- daily doses exceeding 6.5 mg (salt form)/kg ideal (lean) body weight. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese;
- renal insufficiency;
- cumulative dose more than 200 g (salt form);
- elderly;
- impaired visual acuity.

If there is any indication of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks, abnormal colour vision) that are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be stopped immediately. The patient should be closely observed for possible progression of the abnormality. Retinal changes (and visual disturbances) may progress even after cessation of the therapy (see ADVERSE REACTIONS).

Methods recommended for early diagnosis of retinopathy consist of (1) funduscopy examination of the macula for fine pigmentary disturbances or loss of the foveal reflex and (2) examination of the central visual field with a small red test object for pericentral or paracentral scotoma or determination of retinal thresholds to red. Any unexplained visual symptoms, such as light flashes or streaks also should be regarded with suspicion as possible manifestations of retinopathy.

Psychiatric:

Suicidal behaviour has been reported in patients treated with hydroxychloroquine (see ADVERSE REACTIONS).

Skin:

Dermatological reactions to hydroxychloroquine sulfate tablets may occur. It is not recommended for the treatment of psoriasis or porphyria as these conditions may be exacerbated by its use. Observe caution in patients with psoriasis.

Sexual Health:

Fertility

Animal studies showed an impairment of male fertility with chloroquine treatment (see TOXICOLOGY, Reproductive and development toxicity). There are no data in humans.

Special Populations

Pregnancy:

Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. Hydroxychloroquine sulfate tablets should be avoided in pregnancy. It should be noted that the 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 to the foetus.

Embryonic deaths and ocular malformations in the offspring have been reported when pregnant rats received large doses of chloroquine (see TOXICOLOGY, Reproductive and development toxicity).

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-aminoquinolines.

Pediatric Use:

Safety and efficacy has not been established in rheumatoid arthritis or systemic lupus erythematosus in children. Children are especially sensitive to the 4-aminoquinoline compounds. The most reported fatalities follow the accidental ingestion of chloroquine, sometimes in small doses. Patients should be strongly warned to keep these drugs out of the reach of children (see CONTRAINDICATIONS).

Hepatic Impairment:

Hydroxychloroquine sulfate tablets should be used with caution in patients with hepatic disease or alcoholism, in whom a reduction in dosage may be necessary, or in conjunction with known hepatotoxic drugs. Isolated cases of abnormal liver function tests have been reported; fulminant hepatic failure has also been reported.

Renal Impairment:

Observe caution in patients with renal disease, in whom a reduction in dosage may be necessary, as well as in those taking medicines known to affect this organ.

DRUG INTERACTIONS

A table with potential drug interaction with Hydroxychloroquine is included below. Mylan-Hydroxychloroquine should also be used with caution in patients taking medicines which may cause adverse ocular or skin reactions (see WARNINGS AND PRECAUTIONS).

Proper Name	Effect/clinical comment
Agalsidase	There is a theoretical risk of inhibition of intracellular α -galactosidase activity when Mylan-Hydroxychloroquine is co-administered with agalsidase.
Aminoglycoside antibiotics	Mylan-Hydroxychloroquine may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared including potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics.
Amiodarone	There may be an increased risk of inducing ventricular arrhythmias if Mylan-Hydroxychloroquine is used concomitantly with other arrhythmogenic drugs.
Antacids	As with chloroquine, antacids may reduce absorption of Mylan-Hydroxychloroquine so it is advised that a 4 hour interval be observed between Mylan-Hydroxychloroquine and antacid dosing.
Antidiabetic drugs	May enhance the effects of a hypoglycemic treatment, a decrease in doses of antidiabetic drugs may be required.
Antiepileptic drugs	The activity of antiepileptic drugs might be impaired if co-administered with Mylan-Hydroxychloroquine.
Antimalarials known to lower the convulsion threshold	Mylan-Hydroxychloroquine can lower the convulsive threshold. Co-administration of Mylan-Hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.
Arrhythmogenic drugs	There may be an increased risk of inducing ventricular arrhythmias if Mylan-Hydroxychloroquine is used concomitantly with other arrhythmogenic drugs.

Proper Name	Effect/clinical comment
Ciclosporin	An increased plasma ciclosporin level was reported when ciclosporin and Mylan-Hydroxychloroquine were co-administered.
Cimetidine	Mylan-Hydroxychloroquine may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared including inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial.
Digoxin	May result in increased serum digoxin levels; serum digoxin levels should be closely monitored in patients receiving concomitant treatment.
Drugs that prolong QT interval and other arrhythmogenic drugs	Hydroxychloroquine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if Mylan-Hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin (see WARNINGS AND PRECAUTIONS, Cardiovascular, and SYMPTOMS AND TREATMENT OF OVERDOSAGE).
Insulin	May enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin may be required.
Mefloquine	Mylan-Hydroxychloroquine can lower the convulsive threshold. Co-administration of Mylan-Hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.
Moxifloxacin	There may be an increased risk of inducing ventricular arrhythmias if Mylan-Hydroxychloroquine is used concomitantly with other arrhythmogenic drugs.
Neostigmine	Mylan-Hydroxychloroquine may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared including antagonism of effect of neostigmine.

Proper Name	Effect/clinical comment
Praziquantel	Chloroquine has been reported to reduce the bioavailability of praziquantel. Due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for Mylan-Hydroxychloroquine.
Pyridostigmine	Mylan-Hydroxychloroquine may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared including antagonism of effect of pyridostigmine.
Tamoxifen/Drugs known to induce retinal toxicity	An increased risk of toxic retinopathy was reported when Mylan-Hydroxychloroquine was used concurrently with tamoxifen citrate. Concomitant use of Mylan-Hydroxychloroquine with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended (see WARNINGS AND PRECAUTIONS, Ophthalmologic).
Vaccine: Human diploid cell rabies vaccine	Mylan-Hydroxychloroquine may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared including reduction of the antibody response to primary immunization with intradermal human diploid cell rabies vaccine.

ADVERSE REACTIONS

The following Council for International Organizations of Medical Sciences (CIOMS) frequency rating is used, when applicable: Very common $\geq 10\%$; Common ≥ 1 and $<10\%$; Uncommon ≥ 0.1 and $<1\%$; Rare ≥ 0.01 and $<0.1\%$; Very rare $<0.01\%$; Not known (frequency cannot be estimated from available data).

Blood and lymphatic system disorders

Not known: Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, thrombocytopenia (see WARNINGS AND PRECAUTIONS).

Cardiac disorders

Not known: Cardiomyopathy, which may result in cardiac failure and in some cases a fatal outcome.

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

discontinuation may lead to recovery (see WARNINGS AND PRECAUTIONS, SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Hydroxychloroquine prolongs the QT interval. Ventricular arrhythmias and torsade de pointes have been reported in patients taking Hydroxychloroquine (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Ear and labyrinth disorders

Uncommon: Vertigo, tinnitus

Not known: Hearing loss including cases of irreversible hearing loss.

Eye disorders

Common: Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible (see WARNINGS AND PRECAUTIONS).

Uncommon: Maculopathies which may be irreversible.

Retinopathy with changes in pigmentation and visual field defects. In its early form it appears reversible upon discontinuation of the drug. If allowed to develop however, there may be a risk of progression even after treatment withdrawal.

Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas, abnormal colour visions, reduction in visual acuity, night blindness, difficulty reading and skipping words.

Corneal changes including edema and opacities. They are either symptomless or may cause disturbances such as halos around lights especially at night, blurring of vision or photophobia. They may be transient or are reversible upon discontinuation of therapy (see WARNINGS AND PRECAUTIONS).

Not known: Macular degeneration which may be irreversible.

Gastrointestinal disorders

Very common: Abdominal pain, nausea

Common: Diarrhea, vomiting

These symptoms usually resolve immediately upon reducing the dose or upon stopping the treatment.

Hepatobiliary disorders

Uncommon: Abnormal liver function tests

Not known: Fulminant hepatic failure (see WARNINGS AND PRECAUTIONS)

Immune system disorders

Not known: Urticaria, angioedema, bronchospasm.

Metabolism and nutrition disorders

Common: Anorexia (usually resolves immediately upon reducing the dose or upon stopping the treatment).

Not known: hypoglycemia (see WARNINGS AND PRECAUTIONS).

Mylan-Hydroxychloroquine may exacerbate porphyria (see WARNINGS AND PRECAUTIONS).

Musculoskeletal and connective tissue disorders

Uncommon: Sensory motor disorders

Not known: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Depression of tendon reflexes, abnormal results of nerve conduction tests. Myopathy may be reversible after drug discontinuation, but recovery may take many months (see WARNINGS AND PRECAUTIONS).

Nervous system disorders

Common: Headache

Uncommon: Dizziness

Not known: Convulsions. Extrapyramidal reactions such as: akathisia, dystonia, dyskinesia, gait disturbance, tremor.

Psychiatric disorders

Common: Affect lability

Uncommon: Nervousness

Not known: Psychosis, suicidal behavior.

Skin and subcutaneous tissue disorders

Common: Skin rash, pruritus

Uncommon: Pigmentary changes in skin and mucous membranes, bleaching of hair, alopecia. These usually resolve readily upon cessation of therapy.

Not known: Bullous eruptions (including urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum), toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), photosensitivity, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP).

AGEP has to be distinguished from psoriasis, although Mylan-Hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favorable after discontinuation of drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2 grams having proved fatal.

Symptoms:

The 4-aminoquinoline compounds are very rapidly and completely absorbed following ingestion and in accidental overdose toxic symptoms may occur within 30 minutes. These consist of headache, drowsiness, visual disturbances, cardiovascular collapse, hypokalemia and convulsions, rhythm and conduction disorders, including QT prolongation, torsade de pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after overdose. The ECG may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Treatment:

Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital), or gastric lavage until the stomach is completely emptied. If finely powdered activated charcoal is introduced by the stomach tube, after lavage and within 30 minutes after ingestion of the tablets, it may inhibit further intestinal absorption of the drug. To be effective, the dose of activated charcoal should be at least five times the estimated dose of ingested hydroxychloroquine. Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultrashort-acting barbiturate may be tried but, if due to anoxia, convulsions should be corrected by oxygen administration, artificial respiration or, in shock with hypotension, by vasopressor therapy. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, has also been advised. Exchange transfusions have been used to reduce the level of 4-aminoquinolines in the blood.

Consideration should be given to administering diazepam parenterally since studies have reported it beneficial in reversing chloroquine cardiotoxicity.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 hours. Fluids may be forced, and sufficient ammonium chloride may be administered for a few days to acidify the urine to help promote urinary excretion.

If serious toxic symptoms occur from overdose or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) three or four days a week be administered for several months after therapy has been stopped, as acidification of the urine increases renal excretion of the 4-aminoquinoline compounds by 20 to 90 percent. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Absolute body weight used as a guide to dosage could result in an overdose; daily doses should not exceed 6.5 mg (salt form)/kg ideal (lean) body weight. Exceeding the recommended daily dose sharply increase the risk of retinal toxicity.

The dosages cited below are stated in terms of hydroxychloroquine sulfate. One 200 mg tablet is equivalent to 155 mg base. Each dose should be taken with a meal or a glass of milk.

Rheumatoid Arthritis:

The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur somewhat early. Several months of therapy may be required before maximum effects can be obtained. If objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months, the drug should be stopped. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial dosage - *In adults*, from 400 to 600 mg daily. 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 dosage is reduced by 50 percent and continued at an acceptable maintenance level of 200 to 400 mg daily. The incidence of retinopathy has been reported to be higher when the maintenance dose is exceeded.

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

Use in Combination Therapy: Mylan-Hydroxychloroquine (hydroxychloroquine sulfate) 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 hydrocortisone from 5 to 10 mg; of prednisolone and prednisone from 1 to 2.5 mg; of methylprednisolone and triamcinolone from 1 to 2 mg and dexamethasone from 0.25 to 0.5 mg. Regimens of treatment using other agents than steroids and NSAIDs are under development. No definitive dose combinations have been established.

Lupus Erythematosus:

Initially, the average *adult* dose is 400 mg once or twice daily. This may be continued for several weeks or months, depending upon the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200 to 400 mg daily will suffice. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Malaria:

Suppression - *In adults*, 400 mg on exactly the same day of each week. *In children (6 years of age and older)*, the weekly suppressive dose is 5 mg base/kg, but should not exceed the adult dose regardless of body weight.

Suppressive therapy should begin two weeks before exposure. When not administered before exposure, give an initial loading dose of 800 mg to adults, or 10 mg base/kg to children 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 -*In adults*, an initial loading dose of 800 mg followed by 400 mg in six to eight hours. This is followed by 400 mg on each of the next two days for a total of 2 g of hydroxychloroquine sulfate or 1.55 g base. Alternatively, the administration of a single dose of 800 mg has also proved effective. The dosage for adults may also be calculated by body weight.

For children (6 years of age and older) - dosage calculated by body weight is preferred. A total dose representing 25 mg of base/kg is administered over three days as follows:

First dose: 10 mg base/kg (not to exceed 620 mg base)

Second dose: 5 mg base/kg 6 hours after the first dose (not to exceed 310 mg base)

Third dose: 5 mg base/kg 18 hours after the second dose

Fourth dose: 5 mg base/kg 24 hours after the third dose

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

STORAGE AND STABILITY

Store between 15°C - 30°C.

Keep in a safe place out of reach of children.

AVAILABILITY OF DOSAGE FORMS

Each white, film-coated, peanut-shaped tablet, with "HQ 200" debossed on one side and "G" debossed on the other side, is available in bottles of 100 tablets.

The non-medicinal ingredients are maize (corn) starch, calcium hydrogen phosphate dihydrate DC, sodium starch glycollate (Type A), magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol 400, polyethylene glycol 8000.

TOXICOLOGY

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.

Genotoxicity

There are limited data on hydroxychloroquine genotoxicity.

Chloroquine is reported in the literature to be a weak genotoxic agent which may elicit both gene mutations and chromosomal/DNA breaks. Mechanisms may involve DNA intercalation or induction of oxidative stress. Positive and negative results in in vitro reverse gene mutation assays using bacteria (Ames test) and in in vivo studies using rodents (mouse bone marrow cell sister chromatid exchange, mouse bone marrow cell chromosome abnormality, and rat DNA strand-breaks in multiple organs when animals were dosed by intraperitoneal route).

Carcinogenicity

There are no data on hydroxychloroquine carcinogenicity from animal studies and insufficient data on carcinogenicity is available for chloroquine. Both drugs are not classifiable as to their carcinogenicity to humans.

Reproductive and developmental toxicity

There are limited data on hydroxychloroquine teratogenicity.

Supratherapeutic doses of chloroquine resulted in a fetal mortality rate of 25% and ocular malformations in 45% of fetuses. Autoradiographic studies have shown that when administered at the start or the end of gestation, chloroquine accumulates in the eyes and ears.

There are no data on hydroxychloroquine action on fertility.

A study in male rats after 30 days of oral treatment at 5 mg/day of chloroquine showed a decrease in fertility rate, testosterone levels, weight of testes, epididymis, seminal vesicles and prostate, and caused production of abnormal sperm.

^{Pr}MYLAN-HYDROXYCHLOROQUINE

Hydroxychloroquine Sulfate Tablet

200 mg

CONSUMER INFORMATION

Before you begin taking MYLAN-HYDROXYCHLOROQUINE, please read the information in this leaflet carefully and completely. Keep this information with your other health records to read again as necessary.

Keep this medication out of reach of infants and small children. If you think an infant or small child has swallowed even one pill, immediately take them to the nearest hospital emergency room or dial "911" on your telephone.

WHAT YOU NEED TO KNOW BEFORE YOU BEGIN TAKING MYLAN-HYDROXYCHLOROQUINE

- Do not take MYLAN-HYDROXYCHLOROQUINE if you are allergic to hydroxychloroquine sulfate, to any of the other ingredients of MYLAN-HYDROXYCHLOROQUINE or any similar drugs such as chloroquine.
- If you are taking digoxin (a medicine used to treat heart disease) or drugs for diabetes, their dose may need to be reduced.
- Cases of weakening of the heart muscle, resulting in heart failure and in some cases in death, have been reported in patients treated with MYLAN-HYDROXYCHLOROQUINE. Talk to your doctor if you have symptoms such as breathlessness, swelling of the legs, irregular heart beat or fatigue and dizziness.
- MYLAN-HYDROXYCHLOROQUINE crosses the placenta (the organ that allows the mother's oxygen and nutrients to pass to the unborn baby); you should tell your doctor if you are pregnant or planning to get pregnant.
- MYLAN-HYDROXYCHLOROQUINE passes to breast milk; you should tell your doctor if you are breast feeding.
- Do not take MYLAN-HYDROXYCHLOROQUINE if you have retinopathy (eye problem affecting the retina). MYLAN-HYDROXYCHLOROQUINE may cause irreversible damage to the retina (the back of the eye where vision is created). You are required to have an eye exam before taking MYLAN-HYDROXYCHLOROQUINE, then a follow-up as often as needed while taking MYLAN-HYDROXYCHLOROQUINE. You should contact your doctor immediately if you experience any of the following

visual problems: blurred vision, seeing halos around lights, especially at night, seeing light flashes and streaks, night blindness, visual field loss, change in eye colour (eye pigmentation), difficulty focusing eye, difficulty reading (skipped words).

- Talk to your doctor if you have been prescribed both MYLAN-HYDROXYCHLOROQUINE and tamoxifen (a medicine used to treat breast cancer). Both MYLAN-HYDROXYCHLOROQUINE and tamoxifen can individually induce retinal damage (damage to the back of the eye), and taking both drugs at the same time can increase your risk of retinal damage.
- If you experience blurred vision when taking MYLAN-HYDROXYCHLOROQUINE, do not drive or participate in activities requiring alertness.
- MYLAN-HYDROXYCHLOROQUINE can cause hypoglycemia (low blood sugar); sometimes, hypoglycemia may be severe life-threatening, with loss of consciousness or requiring hospitalization. Talk to your doctor if you have symptoms such as sweating, shakiness, weakness, dizziness, fast heartbeat.
- Tell your doctor if you have/are:
 - liver or kidney disease
 - blood disease, including a rare blood disease called porphyria
 - nervous system disease
 - a skin disease called psoriasis
 - a genetic condition known as “glucose-6-phosphate dehydrogenase deficiency”
 - allergic to chloroquine
- Consult your doctor if you suddenly experience fainting spell while using MYLAN-HYDROXYCHLOROQUINE. This medication is known to prolong the QT interval (heart rhythm condition that can potentially cause fast, irregular heartbeats).
- This medication should only be used by the person for whom it is prescribed.
- Protect your skin from the sun with appropriate clothing and sunscreen cream with a minimum SPF 30 rating when going outdoors.

ABOUT MYLAN-HYDROXYCHLOROQUINE

MYLAN-HYDROXYCHLOROQUINE is a white, peanut shaped, normal convex, film-coated tablet with “HQ 200” on one side and “G” on the other.

Each tablet contains 200 mg of hydroxychloroquine sulfate (which is the “active” or “medicinal” ingredient - the part of the tablet that treats the disease or illness).

The non-medicinal ingredients are maize (corn) starch, calcium hydrogen phosphate dihydrate DC, sodium starch glycollate (Type A), magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol 400, polyethylene glycol 8000.

MYLAN-HYDROXYCHLOROQUINE is manufactured by Mylan Pharmaceuticals ULC (toll free # 1-800-575-1379).

WHY MYLAN-HYDROXYCHLOROQUINE IS PRESCRIBED AND ITS EXPECTED EFFECTS

MYLAN-HYDROXYCHLOROQUINE is a medicine available only with a doctor's prescription.

MYLAN-HYDROXYCHLOROQUINE is used for:

- The treatment of **rheumatoid arthritis (RA)**: inflammation of the joints, characterized by stiffness, swelling and pain.
- The treatment of **Systemic Lupus Erythematosus (SLE)**: disease in which the body's immune system mistakenly attacks healthy tissue; it can affect the skin, joints, kidneys, brain, and other organs.
- The treatment of **Discoid Lupus Erythematosus (DLE)**: similar to SLE except it only affects the skin, with symptoms such as red rash or scaly patch.
- The prevention and treatment of acute attacks of certain form of malaria: an infectious disease caused by the presence of parasites in red blood cells, with symptoms such as high fever, shaking, chills, and extreme sweating.

How it works in the body to treat RA, SLE, and discoid lupus is unknown. Optimal improvement from MYLAN-HYDROXYCHLOROQUINE may take up to six months.

HOW TO USE MYLAN-HYDROXYCHLOROQUINE SAFELY

MYLAN-HYDROXYCHLOROQUINE should be taken with a glass of water on a full stomach or a glass of milk to reduce the chance of stomach upset.

If you forget to take a dose, take it as soon as you remember. But if it's within twelve hours of your next dose, skip the one you missed and take only the regularly scheduled dose. **Never take a double dose.**

Take MYLAN-HYDROXYCHLOROQUINE exactly as prescribed by your doctor. -Do not use MYLAN-HYDROXYCHLOROQUINE after expiry date.

Should you have a serious change of health at any point while taking MYLAN-HYDROXYCHLOROQUINE, see your doctor.

If MYLAN-HYDROXYCHLOROQUINE completely controls your disease, talk to your doctor about the possibility of reducing your daily dose. Never reduce the dosage without talking with your doctor first.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MYLAN-HYDROXYCHLOROQUINE can cause side effects. Most side effects are mild to moderate. However, some may be serious and require treatment. Whether you will experience side effects before starting a medication therapy will be unknown to you and your physician. Each person taking a medication has a different experience, depending on their genetic makeup, past and present health status, and lifestyle. Talk to your doctor or pharmacist about any side effect while taking MYLAN-HYDROXYCHLOROQUINE.

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Nausea, stomach pain, stomach cramps	✓		
COMMON			
Diarrhea, loss or lack of appetite (anorexia)		✓	
Vomiting		✓	
Visual problem: blurred vision, difficulty focusing, seeing halos around lights, especially at night, seeing light flashes and streaks, night blindness, visual field loss, change in eye colour (eye pigmentation), difficulty focusing eye, difficulty reading (skipped words)		✓	
Headache	✓		
Rash, itchy rash		✓	
Nervousness, emotional lability		✓	
RARE			
Dizziness	✓		
Hair loss, bleaching of hair, loss of skin pigment or increase in skin pigment (bluish-		✓	

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
black colour)			
Ringing in the ears, decreased hearing		✓	
Nerve and muscle disorders (e.g. tingling, numbness, burning pain, weakness, cramps, and spasms)		✓	
UNKNOWN FREQUENCY			
Severe skin problem			✓
Severe breathing problem (bronchospasm, angioedema)			✓
Increased sensitivity to sunlight. Skin rash due to sunlight can be reduced by appropriate use of sunscreen creams		✓	
Muscle weakness		✓	
Permanent damage to vision		✓	
Heart problems (e.g. breathlessness with exercise or even at rest, swelling of the legs, ankles and feet, irregular heartbeats that feel rapid or pounding, chest pain, sudden fainting)		✓	
Liver problems with symptoms such as: unusual tiredness, nausea, vomiting, abdominal pain, or jaundice (yellow discoloration of the eyes or skin)		✓	
Lowered blood cell counts (e.g. fatigue, weakness, increase susceptibility to infections or bleeding)		✓	

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Convulsions			✓
Psychosis (e.g. hallucinations, loss of contact with reality)		✓	
Suicidal thoughts		✓	
Hypoglycemia (low blood sugar) (e.g. sweating, shakiness, weakness, dizziness, fast heartbeat, nausea, irritability, blurred vision, confusion, loss of consciousness)		✓	
Long-lasting involuntary muscle contraction; impairment of voluntary movements, tremor			✓

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

WHAT TO DO IF YOU OVERDOSE

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdosing on MYLAN-HYDROXYCHLOROQUINE is dangerous; symptoms may occur as early as within 30 minutes after ingestion.

Overdosage with MYLAN-HYDROXYCHLOROQUINE is dangerous particularly in infants, as little as 1-2 grams having proved fatal.

Overdose symptoms include headache, drowsiness, blurred or double vision, rapid heart beats, fainting due to sudden decrease of blood flow and heart pump function, muscle weakness, convulsions and serious trouble breathing.

MYLAN-HYDROXYCHLOROQUINE AND OTHER MEDICATIONS

Talk to your doctor if you are taking or going to take any other medications, including those obtained without prescription, vitamins and natural health products. Some medicines that may interact with MYLAN-HYDROXYCHLOROQUINE are as follows:

- Digoxin. If you are taking both MYLAN-HYDROXYCHLOROQUINE and digoxin, your doctor may decide to check the level of digoxin in your blood.
- Anti-diabetic drugs. If you are taking MYLAN-HYDROXYCHLOROQUINE and are on a medication to control diabetes mellitus [high blood sugar], there is a risk of developing unusually low blood sugar, resulting in hunger pains, rapid heart rate, dizziness, and rarely, loss of consciousness. Your doctor may decide to reduce the doses of medications to control diabetes.
- Antiepileptic drugs
- Some antibiotics used for infections (aminoglycoside antibiotics) such as gentamycin, neomycin, tobramycin
- Neostigmine and pyridostigmine (medicines used to treat muscle disorders)
- Cimetidine (medicine used to treat heartburns)
- Ciclosporine (an immunosuppressant medication)
- Antacids. You should leave a gap of at least 4 hours between taking these medicines and MYLAN-HYDROXYCHLOROQUINE
- Rabies vaccine

- Medicines that may affect the liver, the kidney, the skin or the eye
- Medicines that may cause irregular heart beat (e.g. amiodarone, moxifloxacin) or increase the risk of convulsions (e.g. antimalarials, mefloquine)
- Agalsidase (a medicine used to treat a rare genetic disease called Fabry disease)

Hydroxychloroquine sulfate tablets have been used safely in combination with salicylates (aspirin), non-steroidal anti-inflammatory medications, methotrexate and corticosteroids.

HOW TO STORE MYLAN-HYDROXYCHLOROQUINE

- Keep out of reach and sight of infants and small children.
- Store between 15°C - 30°C.

GENERAL INFORMATION ABOUT MYLAN-HYDROXYCHLOROQUINE

This document can be found at: www.mylan.ca.

The full product monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC, at: 1-844-596-9526

This leaflet was prepared by Mylan Pharmaceuticals ULC, Etobicoke, Ontario M8Z 2S6

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Mylan Pharmaceuticals ULC
Etobicoke, ON M8Z 2S6
1-844-596-9526
www.mylan.ca

PHARMACOLOGY

Mechanism of Action

Rheumatoid Arthritis & Lupus Erythematosus

Hydroxychloroquine has been beneficial for a high percentage of patients with rheumatoid arthritis and systemic lupus erythematosus, especially chronic discoid lupus erythematosus. 4-aminoquinolines such as hydroxychloroquine can affect cellular physiology with anti-inflammatory effects. The mechanism of action is also uncertain but may be mediated by either 1) the inhibition of neutrophil and eosinophil migration, thereby antagonizing histamine and serotonin, or inhibiting prostaglandin synthesis; or 2) interference with intra-cytoplasmic pH thereby disrupting molecular assembly of antigenic peptides resulting in decreased stimulation / down-regulation of autoimmune CD4+ T-cells and autoimmune responses.

Antimalaria

The action of hydroxychloroquine, a 4-aminoquinolone derivative, is similar to the parent drug chloroquine. Originally used as an anti-malarial agent, the exact mechanism of action of hydroxychloroquine has not been fully elucidated. Like chloroquine, hydroxychloroquine is actively concentrated in the digestive vacuoles of plasmodia (malarial parasite) that are residing within erythrocytes. Plasmodicidal action is believed to be achieved through enzyme inhibition (disruption of phospholipid metabolism and increase in pH) and/or interaction with malarial parasite DNA.

Resistance to 4-aminoquinoline derivatives has been reported with increasing frequency in *P. falciparum*. *P. falciparum* that are resistant to chloroquine are also resistant to hydroxychloroquine. The incidence of *P. falciparum* malaria resistance to 4-aminoquinoline derivatives varies geographically and has been reported most frequently in certain parts of China and Southeast Asia, Central and South America, East Africa, and Oceania.

Pharmacokinetics

As a weak base, hydroxychloroquine absorption is complete but rapidly absorbed from the small intestine (GI tract). Extent of absorption may vary depending on inter-subject variability but is not affected by fed or fasted states during dosing. There is no report on the saturability of the absorption processes of hydroxychloroquine. Hydroxychloroquine is about 40-45% protein bound (albumin and α_1 -glycoprotein) and has a bioavailability of approximately 74% (range 70-80%). Following a single oral dose of hydroxychloroquine sulfate 200 mg (1 tablet) to healthy subjects, mean blood peak concentration (C_{max}) of 244 ng/mL (range: 188-427 ng/mL) was achieved within 2-4.5 hours (T_{max}) after dosing. Plasma drug concentrations were found to be about 7 to 8 times lower and more variable than blood concentrations.

The drug is extensively distributed into body tissues with a large apparent volume of distribution (V_d) ($5,500 \pm 2,200$ L and $44,000 \pm 21,000$ L calculated from blood and plasma data respectively). Higher concentrations of the drug were observed in the brain, kidneys, liver, spleen, lung and erythrocytes than in plasma. Both chloroquine and hydroxychloroquine have a high affinity for melanin; thus highest concentrations were observed in the epidermis, retina,

choroid and ciliary body of the eye. Small amounts of hydroxychloroquine (about 3.2 mcg of the drug over 48 hours) were detected in breast milk from a woman given a dose of 800 mg.

Hydroxychloroquine is partially metabolised in the liver. First pass metabolism of the drug is not significant (6%). Metabolism of the drug proceeds by the formation of a series of degradation products which are in the order of 1) the secondary amine, desethylhydroxychloroquine or desethylchloroquine; 2) the primary amine, bisdesethyl-chloroquine; 3) the 4'-aldehyde derivative, a minor portion reduced further to alcohol; and 4) the 4'-carboxy derivative. The major metabolite is desethylhydroxychloroquine, which may also have antiplasmodial activity. Hydroxychloroquine conjugated with glucuronide has been found to be excreted in the bile.

The terminal half-life ($t_{1/2}$) of hydroxychloroquine was estimated from blood data at 50 ± 16 days (about 32 days in plasma) following an oral administration of hydroxychloroquine sulfate 200 mg to healthy volunteers.

Elimination of hydroxychloroquine from the body appears to be gradual and takes place in a biphasic manner. The proportion of the absorbed dose undergoing hepatic metabolism is estimated to be about 30 - 60%. Slow renal clearance of the drug has been reported accounting for 15 to 25% of total clearance and can be detected for several months after discontinuation of the treatment. Following a single dose of hydroxychloroquine sulfate 200 mg, the cumulative urinary excretions of the unchanged drug and its metabolites over a 86 day period were about 16% and 1.3% of the administered dose respectively. Unabsorbed drug (up to 15-24%) is excreted in the feces. Unknown amounts are deposited into dermal cells and sloughed off by the skin. Elimination of the remaining unaccounted amount of the administered dose has been suggested as via hepatic metabolism followed by biliary excretion, and shedding pigmented tissue such as skin. However, some reports indicate that between 21 and 47% of the drug ingested is excreted unchanged.

CLINICAL EFFICACY AND SAFETY STUDIES

Comparative Bioavailability

A single-dose, randomised, two-treatment parallel design bioequivalence study of Mylan-Hydroxychloroquine (200 mg) (Mylan Pharmaceuticals ULC) and Plaquenil® (Hydroxychloroquine Sulphate) 200 mg (Sanofi-Winthrop) was performed in normal healthy subjects (n = 111) was performed under fasted and fed conditions.

A summary of the results is presented in the following table.

Hydroxychloroquine Sulfate 1 x 200 mg From Measured Data Geometric Mean Arithmetic Mean (CV%) Fasted Study				
Parameter	Test*	Reference^	Ratio (%) of Geometric Means	90% Confidence Interval
AUC ₀₋₇₂ (ng.hr/mL)	3941 4152 (32.5)	3858 4066 (34.7)	102	92.1 - 113.3
AUC _t (ng.hr/mL)	5247 5543 (33.8)	5096 5356 (33.5)	103	92.8 - 114.2
C _{max} (ng/mL)	183 194 (33.7)	175 187 (38.9)	105	93.3 - 116.9
T _{max} (h)**	3.40 (41.8)	3.20 (47.3)	n/a	n/a
T _½ (h)**	40.6 (21.0)	39.5 (18.4)	n/a	n/a

*Mylan-Hydroxychloroquine Tablets

^ Plaquenil®* Tablets Sanofi-Synthelabo Canada Inc (formerly Sanofi-Winthrop). (Markham, Ontario). Purchased in Canada.

** Expressed as arithmetic means (CV%)

TABLE 2: SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Hydroxychloroquine Sulfate 1 x 200 mg From Measured - Data Geometric Mean Arithmetic Mean (CV%) Fed Study				
Parameter	Test*	Reference^	Ratio (%) of Geometric Means	90% Confidence Interval
AUC ₀₋₇₂ (ng.hr/mL)	3658 3871 (32.3)	3696 3907 (36.8)	99	88.9 - 110.2
AUC ₁ (ng.hr/mL)	4970 5238 (31.3)	4936 5218 (35.8)	101	90.6 - 111.9
C _{max} (ng/mL)	158 167 (31.9)	167 178 (37.9)	95	85.1 - 106.1
T _{max} (h)**	4.60 (40.4)	4.38 (35.1)	n/a	n/a
T _{1/2} (h)**	40.9 (17.6)	39.2 (19.9)	n/a	n/a

* Mylan-Hydroxychloroquine Tablets

^ Plaquenil®* Tablets Sanofi-Synthelabo Canada, Inc. (formerly Sanofi-Winthrop) (Markham, Ontario) Purchased in Canada.

** Expressed as arithmetic means (CV%)

Rheumatoid Arthritis & Lupus Erythematosus

Overall efficacy of hydroxychloroquine as a lower toxicity anti-rheumatic alternative has been reported on various occasions.

Of 108 rheumatoid arthritis patients treated with hydroxychloroquine (200-400 mg/day) for at least 6 months a 63% response rate has been reported. A similar study reports a 70% response rate with 12% of patients showing complete remission.

In trials comparing 300 patients randomized to hydroxychloroquine and 292 to placebo, a statistically significant benefit was observed with hydroxychloroquine. Overall efficacy appeared to be moderate, but the low toxicity profile of hydroxychloroquine should be considered in the treatment of rheumatoid arthritis.

Hydroxychloroquine (400 mg/day) was also found to be equally effective as intramuscular gold (50 mg/week titrated to response) in the treatment of rheumatoid arthritis. However, hydroxychloroquine demonstrated a beneficial effect on the lipid profiles of patients with rheumatoid arthritis, by significantly increasing high density lipoprotein (HDL) levels by a median 15%.

In a double-blind randomized study, acitretin and hydroxychloroquine were found to be equally effective for the treatment of lupus erythematosus in 58 patients. Acitretin 50 mg/day (n= 28) and hydroxychloroquine 500 mg/day (n=30) was compared with improvement obtained in 46%

and 50% of subjects for acitetrin and hydroxychloroquine respectively. However, the incidence of side effects was significantly higher in the patients administered acitetrin (4 subjects) requiring discontinuation of therapy compared to hydroxychloroquine (0 subjects). Human volunteers demonstrated tolerance to administration of eight tablets (one tablet = 155 to 160 mg) in a single dose, with no more side effects than mild gastrointestinal disturbances lasting for two to ten hours (mean peak plasma level = 635 mcg/L). The primary concern with hydroxychloroquine use is the possibility of retinal toxicity. This maculopathy however is a rare event, with an incidence of < 1 %. There is no evidence that the retinal toxicity of hydroxychloroquine is related to the maximum blood concentration of the drug. The potential risk of maculopathy has been reported to be related to cumulative dose (> 800 g), duration of the treatment (> 10 years), and age (>65 years). A daily dosage of greater than 6.0-6.5 mg/kg, especially in patients with abnormal hepatic or renal function, is also associated with an increased risk. Of 1,207 patients surveyed using hydroxychloroquine, only 6 patients (0.12%) revealed toxicity. Patients receiving < 6.5 mg/kg of the drug daily did not exhibit any definite retinal toxicity due to hydroxychloroquine.

Of ninety-nine patients treated with 400 mg/day hydroxychloroquine sulfate for at least one year (median period of 33 months), only three patients revealed mild retinotoxic effects but no patient sustained permanent visual acuity. A seven year follow-up of these patients revealed no increased incidence or severity of toxic effects.

Both chloroquine and hydroxychloroquine have a high affinity for melanin; thus highest accumulations of the drug in the body are observed in the epidermis and retina, which may account for their retinal toxicity.

However, hydroxychloroquine is preferred to chloroquine because of a lower risk of retinal toxicity. It has been proven that the incidence of retinopathy during hydroxychloroquine treatment is much lower than that with chloroquine in equipotent doses. Occurrences of retinal toxicity with hydroxychloroquine have been found to be almost exclusively at higher than recommended doses. The incidence of retinopathy during hydroxychloroquine treatment appears to be lower than with chloroquine given in equipotent doses, however, lower efficacies have also been reported. In man, the lethal dose of chloroquine has been estimated at 3-5 g in adults and 0.75-1 g in young children.

Antimalaria

The action of this compound against malarial parasites resembles that of chloroquine.

TOXICOLOGY

Acute Toxicity

	Route of Administration	Acute LD50 mg/base/kg
Mouse	Intravenous	45 ± 2
	Intraperitoneal	182
	Oral	1,880 ± 133
Dog	Intramuscular	> 25
Rabbit	Intravenous	12.4

Signs of Toxicity: Rapid onset of hypoventilation, cardiovascular collapse with bradycardia, peripheral vasodilation, arrhythmias and convulsions.

Subacute and Chronic Toxicity

In rats, a five day oral dose test reported a tolerated daily dose greater than 250 mg/kg and less than 400 mg/kg.

Hydroxychloroquine was administered 6 days a week for 13 weeks in dogs. It was found that dogs readily tolerated oral doses of 20 mg/ kg of hydroxychloroquine. A similar study using chloroquine killed three out of four animals within 19 days.

A ten month study in monkeys demonstrated a tolerated daily oral dose of more than 60 mg/base/kg.

Hydroxychloroquine appeared to generally be less toxic than chloroquine in animal toxicity studies, however, this was associated with lower tissue levels of drug.

Special Toxicity Studies

Reproduction / Teratogenicity

Hydroxychloroquine crosses the placental barrier in mice and shows affinity for melanin containing tissues such as retina, iris and choroid of the eye.

Carcinogenicity / Mutagenicity

Reports of related carcinogenic or mutagenic actions of hydroxychloroquine have not been well documented.

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