PRODUCT MONOGRAPH

NU-HYDROXYQUINE

Hydroxychloroquine Sulfate Tablets USP

200 mg (Expressed as the salt)

Equivalent to 155 mg Hydroxychloroquine

Anti-rheumatic, Antimalarial

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200 mg (Expressed as the salt)
Equivalent to 155 mg Hydroxychloroquine

THERAPEUTIC CLASSIFICATION

Anti-rheumatic, Antimalarial

ACTIONS AND CLINICAL PHARMACOLOGY

Hydroxychloroquine is highly active against the erythrocytic forms of *P. vivax* and *malariae* and most strains of *P. falciparum* (but not the gametocytes of *P. falciparum*). It also exerts a beneficial effect in patients with lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis. The precise mechanism of action in these diseases is unknown.

Hydroxychloroquine does not prevent relapses in patients with *vivax* or *malariae* malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent *vivax* or *malariae* infection when administered as a prophylactic. It is however, highly effective as a suppressive agent in patients with *vivax* or *malariae* malaria, in terminating acute attacks, and in significantly lengthening the interval between treatment and relapse. In patients with *falciparum* malaria, it abolishes an acute attack and effects a complete cure of the infection, unless due to a resistant strain of *P. falciparum*.

Comparative Bioavailability

Two comparative bioavailability studies were performed in healthy human volunteers - one under fasting conditions and one with food. The rate and extent of absorption of hydroxychloroquine was measured and compared following oral administration of a 200 mg dose of Nu-hydroxyquine or Plaquenil 200 mg tablets. The results from measured data are summarized as follows:

Fasting Study: Summary Table of the Comparative Bioavailability Data
Hydroxychloroquine Sulfate (Dose: 1x200 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Nu-hydroxyquine	Plaquenil®†	
AUC_{0-72} (ng•hr/mL)	3911 4039 (25)	3772 3991 (35)	106
C_{max} (ng/mL)	194 202 (29)	195 209 (39)	101
T_{max} (hr)*	3.46 (52)	2.84 (43)	-

AUC_{0-72}: Area under the drug concentration versus time curve from time 0 to 72 hours.
C_{max}: The observed maximum or peak concentration of the drug.
T_{max}: The time after administration of the drug at which C_{max} is observed.
* Arithmetic means (CV%).
** Based on the least squares estimate.
† Plaquenil® (Sanofi Winthrop Canada) was purchased at a Canadian retail pharmacy.

Fed Study: Summary Table of the Comparative Bioavailability Data
Hydroxychloroquine Sulfate (Dose: 1x200 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Nu-hydroxyquine	Plaquenil®†	
AUC_{0-72} (ng•hr/mL)	4090 4267 (29)	4216 4480 (38)	97
C_{max} (ng/mL)	189 199 (32)	192 206 (39)	99
T_{max} (hr)*	4.06 (35)	4.21 (40)	-

AUC_{0-72}: Area under the drug concentration versus time curve from time 0 to 72 hours.
C_{max}: The observed maximum or peak concentration of the drug.
T_{max}: The time after administration of the drug at which C_{max} is observed.
* Arithmetic means (CV%).
** Based on the least squares estimate.
† Plaquenil® (Sanofi Winthrop Canada) was purchased at a Canadian retail pharmacy.

Note: the sampling time was not long enough in the above studies to determine elimination half life ($t_{1/2}$). However, the terminal half life of the drug was estimated in another unrelated study to

average 50 and 32 days respectively in the blood and plasma of healthy volunteers given 200 mg of hydroxychloroquine sulfate orally.

INDICATIONS AND CLINICAL USE

NU-HYDROXYQUINE (hydroxychloroquine sulfate) is indicated for use in patients with the following disorders who have not responded satisfactorily to drugs with less potential for serious side effects: lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis.

NU-HYDROXYQUINE is also indicated for the suppressive treatment of malaria and the treatment of acute attacks of malaria due to *Plasmodium vivax, P. malariae, P. ovale* and susceptible strains of *P. falciparum*.

CONTRAINDICATIONS

The use of NU-HYDROXYQUINE (hydroxychloroquine sulfate) is contraindicated:

– In the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound,

– In patients with known hypersensitivity to 4-aminoquinoline compounds.

WARNINGS

Use in Children

The safety and efficacy of hydroxychloroquine have not been fully established in rheumatoid arthritis or systemic lupus erythematosus in children. Young children are particularly sensitive to

the toxic effects of 4-aminoquinones, therefore patients should be warned to keep hydroxychloroquine out of reach of children. Fatalities following the accidental ingestion of chloroquine, sometimes in small doses (0.75 or 1 g in one 3 year old child) have been reported.

Retinal Damage

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. Retinopathy has been reported to be dose related.

When prolonged high dose therapy with any antimalarial compound is contemplated, initial (baseline) and periodic (every three months) ophthalmic examinations (including visual acuity, expert slit-lamp, fundoscopic, and visual field tests) should be performed.

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) 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 even after cessation of therapy.

Neuromuscular/Muscular Changes

All patients on long-term high dose 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.

Use in Patients with Psoriasis/Porphyria

Use of hydroxychloroquine in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria, the condition may be exacerbated. Hydroxychloroquine should not be used in these conditions unless in the judgement of the physician the benefit to the patient outweighs the possible hazard.

Pregnancy and Lactation

Usage of this drug during pregnancy and breast-feeding should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the possible hazard. It should be noted that radioactively-tagged chloroquine administered i.v. to pregnant, pigmented CBA mice passed rapidly across the placenta. It accumulated selectively in the melanin structures of the fetal eyes and was retained in the ocular tissues for 5 months after the drug had been eliminated from the rest of the body. It is also known to be excreted in breast milk and that infants are sensitive to 4-aminoquinolines.

In patients taking hydroxychloroquine for systemic or discoid lupus erythematosus or rheumatoid arthritis who are planning a pregnancy and wish to minimize drug exposure to the fetus, the 40 day half-life and large volume of distribution of the drug requires about 6 months cessation of therapy before conception. Cessation of therapy is associated with a risk of exacerbation of disease. In patients already taking hydroxychloroquine for systemic lupus erythematosus at the time they become pregnant, discontinuation of the drug may increase the risk to the fetus because of reactivation of the disease. Although safety data are limited, at least for SLE, consideration may be given to continuing hydroxychloroquine. For RA, the arthritis may improve during therapy, allowing consideration for stopping the hydroxychloroquine, but there is a risk of post-partum flare.

Treatment and Prevention of Malaria

NU-HYDROXYQUINE (hydroxychloroquine sulfate) is not effective against chloroquine-resistant strains of *P. falciparum*. In recent years it has been found that certain strains of *P. falciparum* located in certain parts of the world have become resistant to 4-aminoquinoline compounds (including hydroxychloroquine) as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia. Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strain of parasites.

Treatment of Rheumatoid Arthritis

In the treatment of rheumatoid arthritis, if objective improvement (such as reduced joint swelling, increased mobility) does not occur within 6 months, the drug should be discontinued. Safe use of the drug in the treatment of juvenile arthritis has not been established.

PRECAUTIONS

Dermatological reactions to hydroxychloroquine may occur, and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

The methods recommended for early diagnosis of “chloroquine retinopathy” consist of (1) fundoscopic 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.

For treatment of serious toxic symptoms, see Symptoms and Treatment of Overdosage.

Laboratory Tests

Periodic blood cell counts should be made if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuation of the drug should be considered. The drug should be administered with caution in patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.

Drug Interactions

NU-HYDROXYQUINE (hydroxychloroquine sulfate) should be used with caution with known hepatotoxic drugs and in alcoholics or patients with hepatic or renal disease. Concomitant use of medicaments including phenylbutazone, gold, and other drugs known to cause sensitization and dermatitis should be avoided. Digoxin levels may be increased by hydroxychloroquine and should therefore be monitored. Hydroxychloroquine interferes with antibody response to human diploid rabies vaccine.

ADVERSE REACTIONS

Malaria

Following administration in doses adequate for malarial suppression or the treatment of an acute malarial attack, mild and transient headache, dizziness, and gastrointestinal complaints (diarrhea, anorexia, nausea, abdominal cramps and, on rare occasions, vomiting) may occur.

Lupus Erythematosus and Rheumatoid Arthritis

Not all of the following reactions have been observed during long-term therapy with every 4-aminoquinoline compound, but they have been reported with at least one of them and should be borne in mind when drugs of this class are administered. Adverse effects with different compounds vary in type and frequency.

CNS Reactions: Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia.

Neuromuscular Reactions: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction.

Ocular Reactions

A. *Ciliary body:* Disturbance of accomodation with symptoms of blurred vision. This reaction is dose-related and reversible with cessation of therapy.

B. *Cornea:* Transient edema, punctate to lineal opacities, decreased corneal sensitivity. The corneal changes, with or without accompanying symptoms (blurred vision, halos around lights, photophobia), are fairly common, but reversible. Corneal deposits may appear as early as three weeks following initiation of therapy.

   The incidence of corneal changes and visual side effects appears to be considerably lower with hydroxychloroquine than with chloroquine.

C. *Retina: Macula:* Edema, atrophy, abnormal pigmentation (mild pigment stippling to a "bull's-eye" appearance), loss of foveal reflex, increased macular recovery time following exposure to a bright light (photo-stress test), elevated retinal threshold to red light in macular paramacular and peripheral retinal areas.

Other fundus changes include optic disc pallor and atrophy, attenuation of retinal arterioles, fine granular pigmentary disturbances in the peripheral retina and prominent choroidal patterns in advanced stage.

D. *Visual field defects:* pericentral or paracentral scotoma, central scotoma with decreased visual acuity, rarely field constriction.

The most common visual symptoms attributed to the retinopathy are: reading and seeing difficulties (words, letters, or parts of objects missing), photophobia, blurred distance vision, missing or blacked out areas in the central or peripheral visual field, light flashes and streaks.

Retinopathy appears to be dose related and has occurred within several months (rarely) to several years of daily therapy; a small number of cases have been reported several years after antimalarial drug therapy was discontinued. It has not been noted during prolonged use of weekly doses of the 4-aminoquinoline compounds for suppression of malaria.

Patients with retinal changes may have visual symptoms or may be asymptomatic (with or without visual field changes). Rarely scotomatous vision or field defects may occur without obvious retinal change.

Retinopathy may progress even after the drug is discontinued. In a number of patients, early retinopathy (macular pigmentation sometimes with central field defects) diminished or regressed completely after therapy was discontinued. Paracentral scotoma to red targets (sometimes called "premaculopathy") is indicative of early retinal dysfunction which is usually reversible with cessation of therapy.

A small number of cases of retinal changes have been reported as occurring in patients who received only hydroxychloroquine. These usually consisted of alteration in retinal pigmentation which was detected on periodic ophthalmologic examination; visual field defects were also present in some instances. A case of delayed retinopathy has been reported with loss of vision starting 1 year after administration of hydroxychloroquine had been discontinued.

Dermatologic Reactions: Bleaching of the hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis.

Hematologic Reactions: Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency).

Gastrointestinal Reactions: anorexia, nausea, vomiting, diarrhea, and abdominal cramps.

Miscellaneous Reactions: isolated cases of abnormal liver function and fulminant hepatic failure, weight loss, lassitude, exacerbation or precipitation of porphyria and non-sensitive psoriasis. Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The 4-aminoquinoline compounds are very rapidly and completely absorbed after ingestion, and in accidental overdosage, or rarely with lower dosages in hypersensitive patients, toxic symptoms may occur within 30 minutes. These consist of headache, drowsiness, visual disturbances, cardiovascular collapse, and convulsions, followed by sudden and early respiratory and cardiac arrest.

The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

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 hydroxychloroquine ingested. 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, it 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, may also be necessary. Exchange transfusions have been used to reduce the level of 4-aminoquinoline drug in the blood.

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 (8 g daily in divided doses

for adults) may be administered for a few days to acidify the urine to help promote urinary excretion in cases of both overdosage and sensitivity.

If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) be administered orally 3 or 4 days a week for several months after therapy has been stopped, as acidification of the urine increases renal excretion of 4-aminoquinoline compounds by 20 to 90%. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

DOSAGE AND ADMINISTRATION

One tablet of 200 mg of hydroxychloroquine sulfate is equivalent to 155 mg base.

Lupus Erythematosus and Rheumatoid Arthritis

Lupus Erythematosus: Initially, the average *adult* dose is 400 mg (= 310 mg base) once or twice daily. This may be continued for several weeks or months, depending on the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200 mg to 400 mg (= 155 to 310 mg base) daily will frequently suffice.

The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

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 relatively 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 discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial dosage: In adults, from 400 mg to 600 mg (= 310 mg to 465 mg base) daily, each dose to be taken with a meal or a glass of milk. In a small percentage of patients, troublesome side effects may require temporary reduction of the initial dosage. Later (usually from five to ten days), the dose may gradually be increased to the optimum response level, often without return to 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 a usual maintenance level of 200 mg to 400 mg (= 155 to 310 mg base) daily, each dose to be taken with a meal or a glass of milk. The incidence of retinopathy has been to be higher when this maintenance dose is exceeded.

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

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 indicated, it may be done by reducing every 4 to 5 days the dose of cortisone by no more than from 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 of dexamethasone from 0.25 mg to 0.5 mg.

Malaria

Suppression: *In adults*, 400 mg (= 310 mg base) on exactly the same day of each week. *In infants and children*, the weekly suppressive dosage is 5 mg, calculated as base per kg of body weight, but should not exceed the adult dose regardless of weight.

If circumstances permit, suppressive therapy should begin two weeks prior to exposure. However, failing this, in adults, an initial double (loading) dose of 800 mg (= 620 mg base) or in children 10 mg base/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: *In adults*, an initial dose of 800 mg (= 620 mg base), followed by 400 mg (= 310 mg base) in 6 to 8 hours and 400 mg (= 310 mg base) on each of two consecutive days (total 2 g hydroxychloroquine sulfate or 1.55 g base). An alternative method, employing a single dose of 800 mg (=620 mg base) has also proved effective.

The dosage in adults may also be calculated on the basis of body weight but this method is preferred for infants and children.

For infants and children, a total dose representing 32.3 mg hydroxychloroquine sulfate per kg (=25 mg base/kg) of body weight is administered in 3 days as follows:

First dose: 12.9 mg hydroxychloroquine sulfate per kg (10 mg base/kg), but not exceeding a single dose of 800 mg hydroxychloroquine sulfate (= 620 mg base).

Second dose: 6.5 mg hydroxychloroquine sulfate (= 5 mg base/kg), (but not exceeding a single dose of 400 mg hydroxychloroquine sulfate [= 310 mg base]) 6 hours after first dose.

Third dose: 6.5 mg hydroxychloroquine sulfate (= 5 mg base/kg) 18 hours after second dose.

Fourth dose: 6.5 mg hydroxychloroquine sulfate (= 5 mg base/kg) 24 hours after third dose.

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

PHARMACEUTICAL INFORMATION

Drug Substance

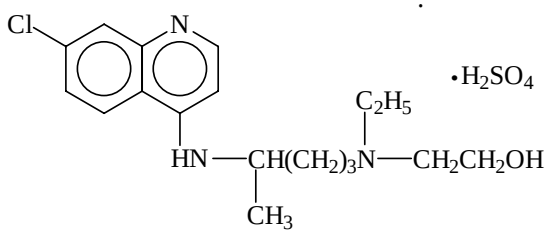
Proper/Common Name: Hydroxychloroquine sulfate

Chemical Names:

1) Ethanol, 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]-sulfate (1:1) salt;

2) 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino]ethanol sulfate (1:1) (salt).

Structural Formula:



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

Molecular Weight: 433.95

Description: Hydroxychloroquine sulfate is a white or practically white, crystalline powder. It is odorless and has a bitter taste. Its aqueous solution has a pH of about 4.5. It is freely soluble in water; practically insoluble in alcohol, chloroform and ether.

Composition

In addition to hydroxychloroquine sulfate, each tablet contains the non-medicinal ingredients croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

Stability and Storage Recommendations

Store at controlled room temperature (15–30°C).

AVAILABILITY OF DOSAGE FORMS

NU-HYDROXYQUINE 200 mg: Each white, capsule-shaped, biconvex film-coated tablet engraved 'HCQ 200' on one side contains hydroxychloroquine sulfate 200 mg. Available in bottles of 100 and 500 tablets, unit dose packages of 30 and 100 tablets.

INFORMATION FOR THE PATIENT

FACTS ON NU-HYDROXYQUINE

(Hydroxychloroquine Sulfate Tablets USP)

Hydroxychloroquine (hye-drox-ee-KLOR-oh-kwin) belongs to the family of medicines called antimalarials.

This medicine is used to prevent and to treat mosquito-generated malaria infection which is contracted in tropical countries. It is also used in the treatment of arthritis to help relieve inflammation, swelling, stiffness, and joint pain and to help control the symptoms of lupus erythematosus (lupus; SLE).

This medicine may be given alone or with one or more other medicines.

Hydroxychloroquine is available only with your doctor's prescription.

BEFORE USING THIS MEDICINE

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This is a decision you and your doctor will make. For hydroxychloroquine, the following should be considered:

Allergies -- Tell your doctor if you have ever had any unusual or allergic reaction to hydroxychloroquine or chloroquine. Also tell your health care professional if you are allergic to any other substances, such as foods, preservatives, or dyes.

Pregnancy -- Unless you are taking it for malaria, use of this medicine is not recommended during pregnancy. In animal studies, hydroxychloroquine has been shown to cause damage to the central nervous system (brain and spinal cord) of the fetus, including damage to hearing and sense of balance, bleeding inside the eyes, and other eye problems. However, when given in low doses (once a week) to prevent malaria, this medicine has not been shown to cause birth defects or other problems in pregnant women.

Breast-feeding -- A very small amount of hydroxychloroquine passes into the breast milk. It has not been reported to cause problems in nursing babies to date. However, babies and children are especially sensitive to the effects of hydroxychloroquine.

Children -- Children are especially sensitive to the effects of hydroxychloroquine. This may increase the chance of side effects during treatment. Overdose is especially dangerous in children. Taking as few as 3 or 4 tablets (250-milligrams [mg] strength) of chloroquine has resulted in death in small children. Because hydroxychloroquine is so similar to chloroquine, it is probably just as toxic.

Older adults -- Many medicines have not been studied specifically in older people. Therefore, it may not be known whether they work exactly the same way they do in younger adults or if they cause different side effects or problems in older people. There is no specific information comparing use of hydroxychloroquine in the elderly with use in other age groups.

Other medicines -- Although certain medicines should not be used together at all, in other cases 2 different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. Tell your health care professional if you are taking any other prescription or non prescription (over-the-counter [OTC]) medicine.

Other medical problems -- The presence of other medical problems may affect the use of hydroxychloroquine. Make sure you tell your doctor if you have any other medical problems, especially:

– Blood disease (severe) - Hydroxychloroquine may cause blood disorders;

– Eye or vision problems - Hydroxychloroquine may cause serious eye side effects, especially in high doses;

– Glucose-6-phosphate dehydrogenase (G6PD) deficiency - Hydroxychloroquine may cause serious blood side effects in patients with this deficiency;

– Kidney disease - There may be an increased chance of side effects in patients with kidney disease;

– Liver disease - May decrease the removal of hydroxychloroquine from the blood, increasing the chance of side effects;

– Nerve or brain disease (severe), including convulsions (seizures) - Hydroxychloroquine may cause muscle weakness and, in high doses, seizures;

– Porphyria - Hydroxychloroquine may worsen the symptoms of porphyria;

– Psoriasis - Hydroxychloroquine may bring on severe attacks of psoriasis;

– Stomach or intestinal disease (severe) - Hydroxychloroquine may cause dyspepsia or stomach upset.

PROPER USE OF THIS MEDICINE

Take this medicine with meals or milk to lessen possible stomach upset, unless otherwise directed by your doctor.

Keep this medicine out of the reach of children to avoid accidental poisoning.

It is very important that you *take this medicine only as directed.* Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered. To do so may increase the chance of serious side effects.

If you are taking this medicine to help keep you from getting malaria, *keep taking it for the full time of treatment*. If you already have malaria, you should still keep taking this medicine for the

full time of treatment even if you begin to feel better after a few days. This will help to clear up your infection completely. If you stop taking this medicine too soon, your symptoms may return.

Do not give this medication to anyone else and use it as an antimalarial only for the trip for which it has been prescribed.

Hydroxychloroquine works best when you take it on a regular schedule. For example, if you are to take it once a week to prevent malaria, it is best to take it on the same day each week. Or if you are to take 2 doses a day, 1 dose may be taken with breakfast and the other with the evening meal. *Make sure that you do not miss any doses.* If you have any questions about this, check with your health care professional.

Dosing -- The dose of hydroxychloroquine will be different for different patients. Follow your doctor's orders or the directions on the label. The following information includes only the average doses of hydroxychloroquine sulfate. If your dose is different, do not change it unless your doctor tells you to do so.

The number of doses you take each day, the time allowed between doses, and the length of time you take the medicine depend on the medical problem for which you are taking hydroxychloroquine.

For prevention of malaria:

- Adults -- 400 milligrams (mg) of hydroxychloroquine sulfate once every seven days.
- Children -- Dose is based on body weight and must be determined by your doctor. The usual dose is 6.5 mg per kilogram (kg) (2.9 mg per pound) of body weight once every seven days.

For treatment of malaria:

– Adults -- 800 mg as a single dose. This may sometimes be followed by a dose of 400 mg six to eight hours after the first dose, then 400 mg once a day on the second and third days.

– Children -- Dose is based on body weight and must be determined by your doctor. The usual dose is 32.3 mg per kg (14.6 mg per pound) of body weight taken over a period of three days.

For treatment of lupus erythematosus:

– Adults -- The average initial dose is 400 mg once or twice daily.

For treatment of rheumatoid arthritis:

– Adults -- The usual initial dose is 400 – 600 mg daily.

Missed dose -- If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

For patients taking hydroxychloroquine *to prevent malaria:*

– Your doctor may want you to start taking this medicine 1 to 2 weeks before you travel to an area where there is a chance of getting malaria. This will help you to see how you react to the medicine. Also, it will allow time for your doctor to change to another medicine if you have a reaction to this medicine.

– Also, you should keep taking this medicine while you are in the area with malaria and for an additional 8 weeks after you leave the area because the malaria parasite has a complex life cycle and may persist for some time in your body. No medicine will protect you completely from malaria. However, to protect you as completely as possible, *it is important to keep taking this medicine for the full time your doctor ordered.* Also, if fever develops during your travels or within 2 months after you leave the area, *check with your doctor immediately.*

For patients taking hydroxychloroquine *for arthritis or lupus:*

– This medicine must be taken regularly as ordered by your doctor in order for it to help you. It may take several months before you feel the full benefit of this medicine.

Storage -- To store this medicine:

– Keep out of the reach of children. Overdose of hydroxychloroquine is very dangerous in children.

– Store at controlled room temperature (15-30°C).

– Do not store in the bathroom, near the kitchen sink, or in other damp places.

– Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

PRECAUTIONS WHILE USING THIS MEDICINE

Check with your doctor immediately if blurred vision, difficulty in reading, or any other change in vision occurs during or after long-term treatment. Your doctor may want you to have your eyes checked by an ophthalmologist (eye doctor).

If your symptoms do not improve within a few days (or a few weeks or months for arthritis), or if they become worse, check with your doctor.

Hydroxychloroquine may cause blurred vision, difficulty in reading, or other change in vision. It may also cause some people to become dizzy or lightheaded. *Make sure you know how you react to this medicine before you drive, use machines, or do anything else that could be*

dangerous if you are dizzy or are not alert or able to see well. If these reactions are especially bothersome, check with your doctor.

Malaria is spread by mosquitoes. If you are living in, or will be traveling to, an area where there is a chance of getting malaria, the following mosquito-control measures will help to prevent infection:

– If possible, sleep under mosquito netting to avoid being bitten by malaria-carrying mosquitoes.

– Wear long-sleeved shirts or blouses and long trousers to protect your arms and legs, especially from dusk through dawn when mosquitoes are out.

– Apply mosquito repellent to uncovered areas of the skin from dusk through dawn when mosquitoes are out.

SIDE EFFECTS OF THIS MEDICINE

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention. When this medicine is used for short periods of time, side effects usually are rare. However, when it is used for a long time and/or in high doses, side effects are more likely to occur and may be serious.

Check with your doctor immediately if any of the following side effects occur:

Less common: Blurred vision or any other change in vision - this side effect may also occur or get worse after you stop taking this medicine

Rare: Convulsions (seizures); increased muscle weakness; mood or other mental changes; ringing or buzzing ears or any loss of hearing; sore throat and fever, unusual bleeding or bruising; unusual tiredness, weakness

Symptoms of overdose: Drowsiness; headache; increased excitability

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

More common: Diarrhea; difficulty in seeing to read; headache; itching (more common in black patients); loss of appetite, nausea or vomiting; stomach cramps or pain

Less common: Bleaching of hair or increased hair loss; blue-black discoloration of skin, fingernails, or inside of mouth; dizziness or lightheadedness; nervousness or restlessness; skin rash

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with doctor.

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.[1]

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. [2]

Hydroxychloroquine is about 40-45% protein bound (albumin and α1-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. [3,4]

The drug is extensively distributed into body tissues with a large apparent volume of distribution (Vd) (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.[5]

Hydroxychloroquine is partially metabolised in 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.[3]

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. [3,5] 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.[6]

CLINICAL EFFICACY AND SAFETY STUDIES

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.[7]

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.[8]

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%.[9]

In a double-blind randomized study, acitretin and hydroxychloroquine were found to be equally effective for the treatment of lupus erythematosus in 58 patients. Acitetrin 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).[10]

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).[11]

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.[13]

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. [14]

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.[15]

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 that with chloroquine in equipotent doses. Occurrences of retinal toxicity with hydroxychloroquine have been found to be almost exclusively at higher than recommended doses.[16,17,18] The incidence of retinopathy during hydroxychloroquine treatment apears 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.[12]

Antimalaria

The action of this compound against malarial parasites resembles that of chloroquine.[1]

TOXICOLOGY

Acute Toxicity[11]

Species	Route Of Administration	Acute LD_{50} 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.[11]

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.[11]

A ten month study in monkeys demonstrated a tolerated daily oral dose of more than 60 mg/base/kg.[11]

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 or hydroxychloroquine have not been well documented.

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