PRODUCT MONOGRAPH

PRO-HYDROXYQUINE – 200

Hydroxychloroquine Sulfate Tablets USP

200 mg (Expressed as the salt)

Equivalent to 155 mg Hydroxychloroquine

Anti-inflammatory, Antimalarial
ATC Code: P01BA02
Aminoquinolines

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory, Antimalarial

ACTIONS AND CLINICAL PHARMACOLOGY

Hydroxychloroquine belongs to the 4-aminoquinoline class. It 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

PRO-HYDROXYQUINE (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.

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 Pro-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 (%)**
	PRO-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 Cmax 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 (%)**
	PRO-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.

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 Pro-Hydroxyquine (Hydroxychloroquine sulfate) can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced.

Malaria: Hydroxychloroquine 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.

Cardiovascular:
Cases of cardiomyopathy resulting in cardiac failure, in some cases with a fatal outcome, have been reported in patients treated with hydroxychloroquine. Pro -Hydroxyquine 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).

Pro-Hydroxyquine may induce cardiac arrhythmia (see Drug Interaction and SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Hematology:
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.

Metabolism:
Hydroxychloroquine Sulfate 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 PRO-HYDROXYQUINE 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 PRO-HYDROXYQUINE should have their blood glucose level checked and the need for PRO-HYDROXYQUINE treatment reviewed as necessary. In cases of severe hypoglycemia, PRO-HYDROXYQUINE should be discontinued and alternative therapy considered. If patients use PRO-HYDROXYQUINE concomitantly with antidiabetic drugs, a decrease in doses of insulin or antidiabetic drugs may be required as PRO-HYDROXYQUINE may enhance the effects of hypoglycemic treatment (see Drug Interactions section below and ADVERSE REACTIONS).

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.

Neurologic:
Extrapyramidal reactions have been reported in patients taking hydroxychloroquine sulfate (see ADVERSE REACTIONS). Symptoms may persist in some patients after discontinuation of therapy.

Ophthalmic:
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 increase the risk of retinal toxicity.

This examination should be more frequent and adapted to the patient, in the following situations:
- daily doses exceeding 6.5 mg/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;
- 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) funduscopic 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 sulfate

Skin:
Dermatological reactions to Pro-Hydroxyquine 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.

Special Populations
Pregnancy:
Hydroxychloroquine crosses the placenta. Data are limited regarding the use of Pro-Hydroxyquine during pregnancy. Pro-Hydroxyquine 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.

Nursing Mothers:
Careful consideration should be given to using Pro-Hydroxyquine 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:
Pro-Hydroxyquine 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 Pro-Hydroxyquine is included below. Pro-Hydroxyquine 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 intra-cellular α-galactosidase activity when Pro-Hydroxyquine is co-administered with agalsidase.
Aminoglycoside antibiotics	Pro-Hydroxyquine 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 Pro-Hydroxyquine is used concomitantly with other arrhythmogenic drugs.
Antacids	As with chloroquine, antacids may reduce absorption of Pro-Hydroxyquine so it is advised that a 4 hour interval be observed between Pro-Hydroxyquine 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 Pro-Hydroxyquine.
Antimalarials known to lower the convulsion threshold	Pro-Hydroxyquine can lower the convulsive threshold. Co-administration of Pro-Hydroxyquine 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 Pro-Hydroxyquine is used concomitantly with other arrhythmogenic drugs.
Ciclosporin	An increased plasma ciclosporin level was reported when ciclosporin and Pro-Hydroxyquine were co-administered.
Cimetidine	Pro-Hydroxyquine 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.

Proper Name	Effect/clinical comment
Digoxin	May result in increased serum digoxin levels; serum digoxin levels should be closely monitored in patients receiving concomitant treatment.
Insulin	May enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin may be required.
Mefloquine	Pro-Hydroxyquine can lower the convulsive threshold. Co-administration of Pro-Hydroxyquine 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 Pro-Hydroxyquine is used concomitantly with other arrhythmogenic drugs.
Neostigmine	Pro-Hydroxyquine 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.
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 Pro-Hydroxyquine.
Pyridostigmine	Pro-Hydroxyquine 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.
Vaccine: Human diploid cell rabies vaccine	Pro-Hydroxyquine 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 ≥ 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).

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)

Pro-Hydroxyquine 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 behaviour

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 PRO-HYDROXYQUINE 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 overdosage, 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 overdosage 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.

DOSAGE AND ADMINISTRATION

Absolute body weight used as a guide to dosage could result in an overdosage; daily doses should not exceed 6.5 mg/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: PRO-HYDROXYQUINE 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 at controlled room temperature (15 ^{o}C –30^{o}C).
Keep in a safe place out of reach of children.

AVAILABILITY OF DOSAGE FORMS

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

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.

CONSUMER INFORMATION

FACTS ON PRO-HYDROXYQUINE
(Hydroxychloroquine Sulfate Tablets USP)

Generic name: Hydroxychloroquine (hye-drox-ee-KLOR-oh-kwin)
Brand name: PRO-HYDROXYQUINE

Before you begin taking PRO-HYDROXYQUINE, 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 PRO-HYDROXYQUINE

- Do not take PRO-HYDROXYQUINE if you are allergic to hydroxychloroquine sulfate, to any of the other ingredients of PRO-HYDROXYQUINE 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 PRO-HYDROXYQUINE. Talk to your doctor if you have symptoms such as breathlessness, swelling of the legs, irregular heart beat or fatigue and dizziness.
- PRO-HYDROXYQUINE 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.
- PRO-HYDROXYQUINE passes to breast milk; you should tell your doctor if you are breast feeding.
- Do not take PRO-HYDROXYQUINE if you have retinopathy (eye problem affecting the retina). PRO-HYDROXYQUINE 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 PRO-HYDROXYQUINE, then a follow-up as often as needed while taking PRO-HYDROXYQUINE. 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).
- If you experience blurred vision when taking PRO-HYDROXYQUINE, do not drive or participate in activities requiring alertness.
- PRO-HYDROXYQUINE 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

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 PRO-HYDROXYQUINE

PRO-HYDROXYQUINE is a white, capsule-shaped, biconvex film-coated tablet engraved 'HCQ 200' on one side and plain on the other.

Each pill contains 200 mg of hydroxychloroquine sulfate (which is the 'active' or 'medicinal' ingredient – the part of the pill that treats the disease or illness).

Non-medicinal ingredients: croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

WHY PRO-HYDROXYQUINE IS PRESCRIBED AND ITS EXPECTED EFFECTS

PRO-HYDROXYQUINE 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 where a person'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 PRO-HYDROXYQUINE may take up to six months.

HOW TO USE PRO-HYDROXYQUINE SAFE
PRO-HYDROXYQUINE 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 PRO-HYDROXYQUINE exactly as prescribed by your doctor. Do not use PRO-HYDROXYQUINE after expiry date.

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

If PRO-HYDROXYQUINE 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

PRO-HYDROXYQUINE 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 PRO-HYDROXYQUINE.

Serious side effects and what to do about them			
SYMPTOM / SIDE 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-black colour)		√	
Ringing in the ears, decreased hearing		√	
Nerve and muscle disorders (e.g. tingling, numbness, burning pain, weakness, cramps, and spasms)		√	
NOT KNOWN			
Severe skin problem			√
Severe breathing problem (bronchospasm, angioedema)			√
Increased sensitivity to sunlight. Skin rash due to		√	

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to:
    Canada Vigilance Program
    Health Canada, Postal Locator 0701E,
    Ottawa, ON, K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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 PRO-HYDROXYQUINE is dangerous; symptoms may occur as early as within 30 minutes after ingestion.

Overdosage with PRO-HYDROXYQUINE 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.

PRO-HYDROXYQUINE 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 PRO-HYDROXYQUINE are as follows:

- Digoxin. If you are taking both PRO-HYDROXYQUINE and digoxin, your doctor may decide to check the level of digoxin in your blood.
- Anti-diabetic drugs. If you are taking PRO-HYDROXYQUINE and are on a medication to control diabetes mellitus [high blood sugar], there is a risk of developing unusually low blood sugars, 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 PRO-HYDROXYQUINE
- 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)

PRO-HYDROXYQUINE has been used safely in combination with salicylates (aspirin), non steroidal anti-inflammatory medications, methotrexate and corticosteroids.

HOW TO STORE PRO-HYDROXYQUINE

- Keep out of reach of infants and small children.
- Store at controlled room temperature (15°C -30°C).

GENERAL INFORMATION ABOUT PRO-HYDROXYQUINE

This leaflet will not tell you everything you need to know about PRO-HYDROXYQUINE. For more information, please talk to your doctor or pharmacist.

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

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