PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrPLAQUENIL®

Hydroxychloroquine Sulfate Tablets

Tablets, 200 mg, Oral

USP

ATC Code: P01BA02

Anti-Inflammatory – Antimalarial – Aminoquinolines

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RECENT MAJOR LABEL CHANGES

2 Contraindications	09/2020
7 Warnings and Precautions, Hematologic	07/2021
7 Warnings and Precautions, Musculoskeletal	07/2021
7 Warnings and Precautions, Psychiatric	07/2021
7 Warnings and Precautions, Skin	07/2021
7 Warnings and Precautions, 7.1.4 Geriatrics	07/2021
7 Warnings and Precautions, 7.1.1 Pregnant Women	10/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4

1.1 Pediatrics 4

1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

4 DOSAGE AND ADMINISTRATION 5

4.1 Dosing Considerations 5

4.2 Recommended Dose and Dosage Adjustment 5

4.5 Missed Dose 7

5 OVERDOSAGE 7

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 8

7 WARNINGS AND PRECAUTIONS 9

7.1 Special Populations 14

7.1.1 Pregnant Women 14

7.1.2 Breast-feeding 15

7.1.3 Pediatrics 15

7.1.4 Geriatrics 15

8 ADVERSE REACTIONS 15

8.2 Clinical Trial Adverse Reactions 15

8.5 Post-Market Adverse Reactions 18

9 DRUG INTERACTIONS 18
9.2 Drug Interactions Overview 18
9.4 Drug-Drug Interactions 19
9.5 Drug-Food Interactions 24
10 CLINICAL PHARMACOLOGY 24
10.1 Mechanism of Action 24
10.3 Pharmacokinetics 24
11 STORAGE, STABILITY AND DISPOSAL 25
12 SPECIAL HANDLING INSTRUCTIONS 25
PART II: SCIENTIFIC INFORMATION 26
13 PHARMACEUTICAL INFORMATION 26
14 CLINICAL TRIALS 26
15 MICROBIOLOGY 26
16 NON-CLINICAL TOXICOLOGY 26
PATIENT MEDICATION INFORMATION 28

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PLAQUENIL (hydroxychloroquine sulfate tablets) is indicated for:

- the treatment of rheumatoid arthritis, and discoid and systemic lupus erythematosus, in adult patients who have not responded satisfactorily to drugs with less potential for serious side effects.
- the suppressive treatment and treatment of acute attacks of malaria due to *P. vivax, P. malariae, P. ovale,* and susceptible strains of *P. falciparum.* PLAQUENIL 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. PLAQUENIL 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,* PLAQUENIL abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum* (see 7 WARNINGS AND PRECAUTIONS, General, *Malaria*).

1.1 Pediatrics

Pediatrics (< 18 years of age): PLAQUENIL is contraindicated in children below 6 years of age (see 2 CONTRAINDICATIONS). The safety of PLAQUENIL for the treatment of juvenile rheumatoid arthritis has not been established (see 4.2 Recommended Dose and Dosage Adjustment, Rheumatoid Arthritis). The safety and efficacy of PLAQUENIL in children have not been established in rheumatoid arthritis or systemic lupus erythematosus (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical trials of PLAQUENIL did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. PLAQUENIL can prolong the QTc interval, especially in patients with underlying risk factors, which may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Risk factors for torsade de pointes in the general population include the age of ≥ 65 years (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, *Electrocardiogram Changes and Potential for Cardiac Arrhythmias*). Extreme caution should be taken when using PLAQUENIL in geriatric patients aged ≥ 65 years due to the drug toxicity and the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in the elderly (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

PLAQUENIL is contraindicated in:

- Patients with pre-existing retinopathy of the eye.
- Patients with known hypersensitivity to 4-aminoquinoline compounds.
- Patients who are hypersensitive to hydroxychloroquine sulfate or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Children below 6 years of age (200 mg tablets not adapted for weight <35 kg) (see 7.1.3 Pediatrics).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Absolute body weight used as a guide to dosage could result in an overdosage; 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 as well as cardiac arrhythmias (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Ophthalmologic).

- PLAQUENIL should be discontinued if signs and symptoms of cardiomyopathy develop, in patients who develop torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia, severe hypoglycemia, severe blood disorder, muscular weakness, or extrapyramidal reactions. PLAQUENIL dosage may need to be temporarily reduced in patients who develop impaired accommodation and blurring of vision that is not self-limiting (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Driving and Operating Machinery, Endocrine and Metabolism, Hematologic, Musculoskeletal, and Neurologic).

- 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.

4.2 Recommended Dose and Dosage Adjustment

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: PLAQUENIL may be used safely and effectively in combination with corticosteroids, salicylates, NSAIDS, and methotrexate and other second line therapeutic agents. Corticosteroids and salicylates can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is suggested, it may be done by reducing every four to five days, the dose of cortisone by no more than 5 to 15 mg; of 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. 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.

Dosing in Special Populations

Patients with Hepatic Impairment: PLAQUENIL should be used with caution in patients with hepatic impairment; a reduction in dosage may be necessary (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Patients with Renal Impairment: PLAQUENIL should be used with caution in patients with renal impairment; a reduction in dosage may be necessary (see 7 WARNINGS AND PRECAUTIONS, Renal).

Pregnant Women: PLAQUENIL should be avoided in pregnancy except when, in the judgment of the healthcare professional, the individual potential benefits outweigh the potential harms (see 7.1.1 Pregnant Women).

4.5 Missed Dose

If a dose is missed, it should be taken as soon as possible. If the missed dose is within twelve hours of the next dose, the missed dose should be skipped, and the regular dosing schedule should be resumed. The patient should be advised **never to take a double dose** (see 5 OVERDOSAGE).

5 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 interval prolongation, torsade de pointes, ventricular tachycardia, ventricular fibrillation, width-increased QRS complex, PR interval prolongation, bradyarrhythmias, nodal rhythm, atrioventricular block, followed by sudden potentially fatal respiratory and cardiac arrest. **Immediate medical attention is required, as these effects may appear shortly after overdose**.

In the event of acute overdose, the patient should be carefully observed (e.g., ECG monitoring) and given symptomatic and supportive treatment. 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-aminoquiolines 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 200 mg	Black ink, calcium hydrogenophosphate, carnauba wax, corn starch, magnesium

		stearate, Opadry White YS-I-7443 and polyethylene glycol 400.

Description

PLAQUENIL (hydroxychloroquine sulfate tablets) is available as white to off-white, film coated, peanut-shaped tablets, containing 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base), with PLAQUENIL printed in black on one side.

Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

General

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

Malaria
PLAQUENIL 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 (see 1 INDICATIONS).

Carcinogenesis and Mutagenesis

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential (see 16 NON-CLINICAL TOXICOLOGY). In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving-long term treatment.

Cardiovascular

Cardiomyopathy
Cases of cardiomyopathy resulting in cardiac failure, in some cases with a fatal outcome, have been reported in patients treated with PLAQUENIL. **PLAQUENIL 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 is diagnosed (see 5 OVERDOSAGE and 8.2 Clinical Trial Adverse Reactions, Cardiac disorders).

Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias
PLAQUENIL can prolong the PR, QRS and QTc intervals, especially in patients with underlying risk factors. Serious adverse events, including fatal outcomes, have been reported in patients taking PLAQUENIL including ventricular arrhythmias, heart blocks, ventricular fibrillation and

torsade de pointes (see 5 OVERDOSAGE, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 8.2 Clinical Trial Adverse Reactions, Cardiac disorders and 9 DRUG INTERACTIONS).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. **Permanently discontinue PLAQUENIL in patients who develop torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. If cardiac complications due to PLAQUENIL are suspected, treatment should be discontinued.**

PLAQUENIL is not recommended for use in patients with baseline QTc prolongation (e.g., congenital or acquired Long QT Syndrome), second-or third-degree atrioventricular block. Electrolyte imbalances (e.g. hypokalemia/hypomagnesemia/hypocalcemia) must be corrected prior to use. Use of PLAQUENIL should be undertaken with extreme caution in patients with other risk factors for torsade de pointes.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥ 65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Concomitant use with other QTc, PR or QRS interval prolonging drugs should be avoided or undertaken with particular caution (see 9 DRUG INTERACTIONS).

The magnitude of QT, PR or QRS prolongation with PLAQUENIL may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded (see 4 DOSAGE AND ADMINISTRATION and 5 OVERDOSAGE).

Driving and Operating Machinery

Patients should be warned about driving and operating machinery since PLAQUENIL can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced (see 4 DOSAGE AND ADMINISTRATION).

Endocrine and Metabolism

PLAQUENIL 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 PLAQUENIL 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 PLAQUENIL should have their blood glucose level checked and the need for PLAQUENIL treatment reviewed as necessary. In cases of severe hypoglycemia, PLAQUENIL should be discontinued and alternative therapy should be considered. If patients use PLAQUENIL concomitantly with antidiabetic drugs, a decrease in doses of insulin or antidiabetic drugs may be required as PLAQUENIL may enhance the effects of hypoglycemic treatment (see 8.2 Clinical Trial Adverse Reactions and 9 DRUG INTERACTIONS).

Hematologic

Periodic blood counts should be obtained in patients requiring prolonged therapy due to the risk of bone marrow depression, including aplastic anemia, agranulocytosis, leucopenia, or thrombocytopenia (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and 8.2 Clinical Trial Adverse Reactions). If any severe blood disorder appears that is not attributable to the disease under treatment, the drug should be discontinued.

Hemolysis has been reported in patients with glucose-6-phosphate dehydrogenase deficiency. Monitor for hemolytic anemia and observe caution in patients with blood disorders or glucose-6-phosphate dehydrogenase deficiency.

Hepatic/Biliary/Pancreatic

PLAQUENIL 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 as well as fulminant hepatic failure have been reported (see 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations, 8.2 Clinical Trial Adverse Reactions, Hepatobiliary disorders, and 9 DRUG INTERACTIONS).

Use of PLAQUENIL in patients with hepatic impairment as well as with concomitant CYP2C8 or CYP3A4 inhibitors can result in elevation of hydroxychloroquine plasma concentrations, with the magnitude of the effect depending on the degree of hepatic impairment, as well as the enzyme inhibited and the potency of the inhibitor (see 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 9 DRUG INTERACTIONS).

Monitoring and Laboratory Tests

ECG assessments are recommended at baseline and periodically during treatment with PLAQUENIL. More frequent monitoring is recommended if PLAQUENIL is administered to

patients with baseline ECG abnormalities or who are being treated concomitantly with other QTc-, QRS-, or PR-interval prolonging drugs. Monitor electrolytes regularly (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 9 DRUG INTERACTIONS).

Periodic assessment of full blood counts should be performed in patients requiring prolonged treatment with PLAQUENIL (see 7 WARNINGS AND PRECAUTIONS, Hematologic, and 8.2 Clinical Trial Adverse Reactions).

Musculoskeletal

Skeletal muscle myopathy or neuropathy leading to progressive weakness and atrophy of proximal muscle groups, depressed tendon reflexes, and abnormal nerve conduction, have been reported. Muscle and nerve biopsies have demonstrated bodies and muscle fibre atrophy with vacuolar changes. 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 8.2 Clinical Trial Adverse Reactions, Musculoskeletal disorders).

Neurologic

Extrapyramidal reactions have been reported in patients taking PLAQUENIL (see 8.2 Clinical Trial Adverse Reactions, Nervous system disorders). 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 colour 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 PLAQUENIL 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 8.2 Clinical Trial Adverse Reactions, Eye disorders).

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 and psychiatric disorders have been reported in some patients treated with PLAQUENIL (see 8.2 Clinical Trial Adverse Reactions, Psychiatric disorders, and 8.5 Post-Market Adverse Reactions, Psychiatric disorders). Psychiatric side effects typically occur within the first month after the start of treatment with PLAQUENIL and have been reported in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

Renal

PLAQUENIL should be used with 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. During treatment and after discontinuation, monitoring for adverse reactions may be warranted in patients with severe renal impairment or end-stage renal disease (ESRD), given the long half-life of hydroxychloroquine (see 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 9 DRUG INTERACTIONS).

Reproductive Health: Female and Male Potential

Fertility

Animal studies showed an impairment of male fertility with chloroquine treatment (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and developmental toxicity). The data in humans is insufficient for hydroxychloroquine.

Skin

Serious Skin Reactions
Serious adverse reactions have been reported with the use of PLAQUENIL including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Monitor for serious skin reactions, especially in patients receiving a drug that may also induce dermatitis. Advise patients to seek medical attention promptly if they experience signs and symptoms of serious skin reactions such as blisters on the skin, eyes, lips or in the mouth, itching or burning, with or without fever (see 8.2 Clinical Trial Adverse Reactions). Discontinue PLAQUENIL if these severe reactions occur.

Worsening of Psoriasis and Porphyria
PLAQUENIL may cause acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although PLAQUENIL may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. PLAQUENIL 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. Outcome is usually favorable after discontinuation of drug.

7.1 Special Populations

7.1.1 Pregnant Women

PLAQUENIL should be avoided in pregnancy except when, in the judgment of the healthcare professional, the individual potential benefits outweigh the potential harms.

It should be noted that 4-aminoquinolines at 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.

Hydroxychloroquine crosses the placenta. Only limited reproductive toxicity data are available for hydroxychloroquine. However, large doses of chloroquine (with similarities in structure and pharmacological properties) were associated with embryonic deaths and ocular malformations in the offspring of pregnant rats (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and developmental toxicity).

For hydroxychloroquine, when used on long-term therapy with high dosages for auto-immune diseases: observational studies and prospective studies in long-term use with large exposure have not observed an increased risk of congenital malformations or poor pregnancy outcomes. Available epidemiologic and clinical studies have methodological limitations including small sample size and study design.

7.1.2 Breast-feeding

Careful consideration should be given to using PLAQUENIL during breastfeeding, since it is excreted in small amounts (approximately 2% of the maternal dose after bodyweight correction) in human breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines. There are very limited data on the safety in the breastfed infant during hydroxychloroquine long-term treatment. The prescriber should assess the potential risks and benefits of use during breastfeeding, according to the indication and duration of treatment.

Although hydroxychloroquine is excreted in breast milk, the amount is insufficient to confer any protection against malaria to the infant. Separate chemoprophylaxis for the infant is required.

7.1.3 Pediatrics

Safety and efficacy have 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 2 CONTRAINDICATIONS and 5 OVERDOSAGE).

7.1.4 Geriatrics

Clinical trials of PLAQUENIL did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. Nevertheless, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. In general, dose selection in geriatric patients should start with the lowest recommended dose, taking into consideration the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reactions information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 7 WARNINGS AND PRECAUTIONS, Hematologic).

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 5 OVERDOSAGE, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 9 DRUG INTERACTIONS).

PLAQUENIL prolongs the QT, PR and/or QRS intervals which may lead to an arrhythmia. Ventricular arrhythmias and torsade de pointes have been reported in patients taking PLAQUENIL (see 5 OVERDOSAGE, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 9 DRUG INTERACTIONS).

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 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

Uncommon: Maculopathies, which may be irreversible.

Retinopathy with changes in pigmentation and visual field defects (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic). 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, vision disturbances, or photophobia. They may be transient or are reversible upon discontinuation of therapy (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

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 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

PLAQUENIL may exacerbate porphyria (see 7 WARNINGS AND PRECAUTIONS, General).

Musculoskeletal and connective tissue disorders
Uncommon: Sensorimotor 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 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

Nervous system disorders
Common: Headache.

Uncommon: Dizziness.

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

Psychiatric disorders
Common: Affect/emotional lability.

Uncommon: Nervousness, irritability.

Not known: Psychosis, suicidal behavior, suicidal ideation.

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) (see 7 WARNINGS AND PRECAUTIONS, Skin).

8.5 Post-Market Adverse Reactions

Psychiatric disorders

Not known: Depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drugs that Prolong the PR, QRS and/or QTc Intervals
PLAQUENIL has the potential to prolong the PR, QRS and/or QTc intervals in a concentration-related manner (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). Caution is recommended if PLAQUENIL is used concomitantly with other drugs that prolong the PR, QRS and QTc intervals. Current information sources should be consulted for drugs that prolong the QTc interval, the QRS duration, or the PR interval.

Halofantrine should not be administered with PLAQUENIL.

Drugs that Affect Electrolytes
Caution is recommended if PLAQUENIL is used with drugs that have the potential to decrease electrolytes levels. Current information sources should be consulted for drugs that disrupt electrolytes.

A table with potential drug interaction with PLAQUENIL is included below. This list of possible drug interactions is not exhaustive. PLAQUENIL should also be used with caution in patients

taking medicines which may cause adverse ocular or skin reactions (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic and Skin).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 1 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Agalsidase	T	↓ activity of agalsidase	There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when PLAQUENIL is co-administered with agalsidase.
Aminoglycoside antibiotics	T	↑ blocking action	PLAQUENIL 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.
Antacids (e.g. magnesium-containing antacids, kaolin)	T	↓ absorption of hydroxy-chloroquine	As with chloroquine, co-administration with antacids (such as magnesium-containing antacids or kaolin) may result in reduced absorption of PLAQUENIL. Per extrapolation, PLAQUENIL should therefore be administered at least two hours apart from antacids or kaolin.
Antidiabetic drugs and insulin	C	↑ effect of antidiabetic	As PLAQUENIL may enhance the effects of a hypoglycemic treatment, a decrease in doses of antidiabetic drugs or insulin may be required (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).
Antiepileptic drugs	C	↓ activity of antiepileptic	The activity of antiepileptic drugs might be impaired if co-administered with PLAQUENIL.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antimalarial drugs known to lower the convulsion threshold (e.g. mefloquine)	T	↑ risk of convulsions	PLAQUENIL can lower the convulsive threshold. Co-administration of PLAQUENIL with other antimalarial drugs known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.
CYP2C8 and CYP3A4 inducers (e.g. rifampin, St. John's Wort, carbamazepine, phenobarbital)	T	↓ efficacy	Lack of efficacy of PLAQUENIL was reported when rifampin, a CYP2C8 and CYP3A4 strong inducer, was concomitantly administered. Caution is advised (e.g. monitoring for efficacy) when CYP2C8 and CYP3A4 strong inducers (such as rifampin, St. John's Wort, carbamazepine, phenobarbital) are concomitantly administered.
CYP2C8 and CYP3A4 inhibitors (e.g. cimetidine, ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir, gemfibrozil, ritonavir, clarithromycin)	T	↑ exposure of hydroxy-chloroquine	Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for PLAQUENIL. Co-administration of PLAQUENIL with moderate and strong CYP2C8 and CYP3A4 inhibitors (such as, but not limited to, ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir) may result in increased plasma concentrations of hydroxychloroquine. Caution is advised (e.g. monitoring for adverse reactions).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that induce retinal toxicity (e.g. tamoxifen)	C	↑ risk of retinopathy	An increased risk of toxic retinopathy was reported when PLAQUENIL was used concurrently with tamoxifen citrate. Concomitant use of PLAQUENIL with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).
Drugs that prolong the QRS and/or QT interval and other arrhythmogenic drugs (e.g. Class IA, IC and III antiarrhythmics, certain antidepressants, antipsychotics, certain anti-infectives, domperidone, 5-hydroxytryptamine (5-HT)3 receptor antagonists, kinase inhibitors, histone deacetylase inhibitors beta-2 adrenoceptor agonists)	C	↑ risk of arrhythmia	PLAQUENIL prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. There may be an increased risk of inducing ventricular arrhythmias if PLAQUENIL is used concomitantly with other drugs that prolong the QT interval, including, but not limited to, Class IA, IC and III antiarrhythmics; certain antidepressants, antipsychotics, and anti-infectives; domperidone; 5-hydroxytryptamine (5-HT)3 receptor antagonists; kinase inhibitors; histone deacetylase inhibitors beta-2 adrenoceptor agonists (see 5 OVERDOSAGE and 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that affect electrolytes (e.g. loop, thiazide, related diuretics, laxatives, enemas, amphotericin B)	T	↑ risk of arrhythmia	Caution is recommended if PLAQUENIL is used with drugs that have the potential to decrease electrolytes levels, including, but not limited to, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors (see 5 OVERDOSAGE and 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Monitoring and Laboratory Tests).
Neostigmine	T	↓ effect of neostigmine	PLAQUENIL 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/Common name	Source of Evidence	Effect	Clinical comment
P-glycoprotein (P-gp) substrates (e.g. cyclosporine, digoxin, dabigatran)	C	↑ plasma/ serum levels	The inhibitory potential of PLAQUENIL on P-gp substrates has not been evaluated. *In vitro* observations show that all other aminoquinolines tested inhibit P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates when PLAQUENIL is concomitantly administered. Increased plasma cyclosporine levels were reported when cyclosporine and PLAQUENIL were co-administered. Increased digoxin serum levels were reported when digoxin and PLAQUENIL were co-administered. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, cyclosporine, dabigatran) are concomitantly administered.
Praziquantel	T	↓ bioavailability of 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 PLAQUENIL.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Pyridostigmine	T	↓ effect	PLAQUENIL 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	T	↓ antibody response	PLAQUENIL 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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Grapefruit products contain one or more components that strongly inhibit CYP3A4 and can increase plasma concentrations of hydroxychloroquine. Consumption of grapefruit or its juice should be avoided while taking PLAQUENIL.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

PLAQUENIL (hydroxychloroquine sulfate tablets) belongs to the 4-aminoquinoline class. PLAQUENIL 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.

10.3 Pharmacokinetics

Absorption:
Following oral administration, peak blood concentrations is achieved in approximately 4 hours. Oral absolute bioavailability is 79%.

Distribution:
Hydroxychloroquine has a large volume of distribution due to extensive tissue accumulation (5500 L in blood, 44 000 L in plasma), and has been shown to accumulate in blood cells, with a blood to plasma ratio of 7.2. Approximately 50% of hydroxychloroquine is bound to plasma proteins.

Metabolism:
Hydroxychloroquine is mainly metabolized to N-desethylhydroxychloroquine, and two other metabolites in common with chloroquine, desethylchloroquine and bidesethylchloroquine. It can be extrapolated from chloroquine, that hydroxychloroquine could be metabolized *in vitro* by the same CYPs as for chloroquine, i.e. CYP2C8 and CYP3A, and to a lesser extent by CYP2D6.

Elimination:
Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 to 60 days. Approximately 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine.

11 STORAGE, STABILITY AND DISPOSAL

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

Keep in a safe place out of reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

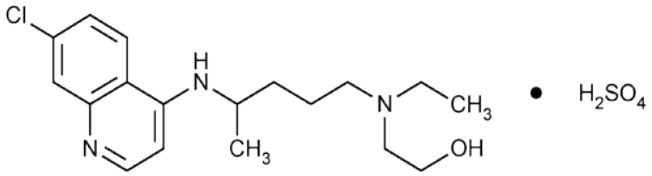
Proper name: Hydroxychloroquine sulfate

Chemical name: (*RS*)-2-*N*-[4-(7-chloro-4-quinolylamino)pentyl]-*N*-ethylaminoethanol sulfate
Ethanol, 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]-ethylamino]-, (±), sulfate (1:1)
(±)-2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]-ethylamino]ethanol sulfate (1:1)

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

Molecular mass: 433.95

Structural formula:



Physicochemical properties: White or practically white crystalline powder, odorless or almost odorless. Solubility: freely soluble in water, practically insoluble in chloroform, in ethanol (96%) and in ether. Melting point: about 240°C.

14 CLINICAL TRIALS

Not applicable.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

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.

Genotoxicity:

Based on the standard genotoxicity studies conducted, hydroxychloroquine is not considered to present a genotoxic risk to humans at therapeutic concentrations.

Hydroxychloroquine is not mutagenic in the bacterial reverse mutation test (i.e., five strains using the Ames test). At therapeutic concentrations of hydroxychloroquine (below 60 µg/mL), clastogenicity or aneugenicity were not observed in the *in vitro* micronucleus test using primary human lymphocytes. However, at concentrations at or above 60 µg/mL of hydroxychloroquine, clastogenicity/aneugenicity potency was observed at the 24+24 hours condition treatment of the *in vitro* micronucleus test. At hydroxychloroquine doses used up to 1000 mg/kg, clastogenicity or aneugenicity were not observed in the *in vivo* micronucleus test following oral administration in rats.

Reproductive and Developmental Toxicology:
There are limited data on hydroxychloroquine reproductive toxicity, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the two products.

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 limited 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 testosterone levels, weight of testes, epididymis, seminal vesicles and prostate, and caused production of abnormal sperm. The fertility rate was also decreased in another rat study after 14 days of intraperitoneal treatment at 10 mg/kg/day of chloroquine.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPLAQUENIL®

Hydroxychloroquine Sulfate Tablets

Read this carefully before you start taking **PLAQUENIL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PLAQUENIL**.

What is PLAQUENIL used for?

PLAQUENIL is used in adults to:

- Treat **Rheumatoid Arthritis (RA)**: a disease marked by stiffness, swelling and pain in your joints.
- Treat **Systemic Lupus Erythematosus (SLE)**: a disease where your immune system attacks healthy parts of your body by mistake. It can affect your skin, joints, kidneys, brain, and other organs.
- Treat **Discoid Lupus Erythematosus (DLE)**: a disease similar to SLE. DLE only affects your skin with red rash or scaly patches.

PLAQUENIL is used in patients 6 years of age and older to:

- Prevent and treat certain forms of **Malaria**: an infection caused by parasites in your red blood cells. Symptoms can include high fever, shaking, chills, and extreme sweating.

You can only get PLAQUENIL with a doctor's prescription.

How does PLAQUENIL work?

It is not known how PLAQUENIL works in the body to treat RA, SLE, and DLE. PLAQUENIL may take up to six months to take effect. For malaria, PLAQUENIL works by killing the parasite that causes the infection.

What are the ingredients in PLAQUENIL?

Medicinal ingredient: hydroxychloroquine sulfate.
Each 200 mg tablet contains 155 mg of hydroxychloroquine as the base.

Non-medicinal ingredients: black ink, calcium hydrogenophosphate, carnauba wax, corn starch, magnesium stearate, Opadry White YS-I-7443 and polyethylene glycol 400.

PLAQUENIL comes in the following dosage forms:

Tablets, 200 mg.

Do not use PLAQUENIL if:

- you are allergic to
    - hydroxychloroquine sulfate
    - any of the other ingredients of PLAQUENIL
    - any similar drugs such as chloroquine
- you have retinopathy. This is an eye problem affecting the retina at the back of your eye. PLAQUENIL may cause irreversible damage to your retina. You should tell your doctor right away if you have any **Visual Problems**.
- you are a child below 6 years of age **or** weigh less than 35 kg.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PLAQUENIL. Talk about any health conditions or problems you may have, including if you:

- were born with, now have, or have a family history of long QT interval. PLAQUENIL may cause **Heart Rhythm Disorders** in some patients. These **Heart Rhythm Disorders** can be seen on an ECG, or an electrical recording of the heart. Caution should be taken when taking PLAQUENIL if you:
    - have heart disease, which can include heart failure, slow heartbeat, heart palpitations or irregular heartbeat. The risk of heart problems may increase with higher doses of PLAQUENIL.
    - have had a heart attack (myocardial infarction)
    - have a family history of sudden death from heart attack before the age of 50
    - take other drugs that can cause prolonged QT interval or are known to affect the rhythm of your heart
- have mental health problems.
- have a low level of potassium, calcium or magnesium in your blood, or have a condition that may affect the levels of those salts in the blood. Examples are an eating disorder or prolonged vomiting.
- are allergic or sensitive to a drug called to quinine.
- are pregnant, or you are planning to get pregnant. PLAQUENIL may be passed to your unborn baby. PLAQUENIL may harm your unborn baby. Your doctor will evaluate the benefit and risk of using PLAQUENIL during pregnancy.

- are breastfeeding. PLAQUENIL passes into breast milk in small amounts. Infants can be very sensitive to the toxic effects of drugs like PLAQUENIL. There is not enough PLAQUENIL in breast milk to protect an infant against malaria. The infant should receive their own malaria treatment if necessary. Talk to your doctor about the risks PLAQUENIL can have on your baby. These risks depend on:
    - why you are taking PLAQUENIL;
    - how long you will be taking PLAQUENIL for.
- have diabetes or symptoms of **low blood sugar**. PLAQUENIL can cause low blood sugar, and sometimes, low blood sugar can be very dangerous. You may pass out or need to go to the hospital.
- have liver or kidney disease.
- have alcoholism.
- have a blood disease, including a rare blood disease called porphyria. PLAQUENIL can make this worse.
- have a skin problems or diseases such as psoriasis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome).
- have nervous system problems or disease.
- Have bone marrow problems that cause low counts of blood platelets, and white and red blood cells
- have a genetic red blood cell disease known as “glucose-6-phosphate dehydrogenase deficiency”.
- have gastrointestinal disorders. These are problems in the intestines, stomach, or gut.
- have decreased vision.
- have muscle, tendon or nerve problems, including muscle weakness.
- have mood problems, including thoughts of suicide or depression.
- are 65 years old or older. There is a higher chance of side effects when this age group takes PLAQUENIL.

Other warnings you should know about:

PLAQUENIL can cause **long QT interval** or **torsade de pointes**. This is a dangerously fast heart rate. It can lead to cardiac arrest, sudden collapse and death.

Heart problems or failure, cardiomyopathy, an enlarged or weak heart can occur if you take PLAQUENIL for long periods of time. These are serious and can result in death. Your doctor will check your heart regularly.

PLAQUENIL can cause **mental health problems** such as abnormal thoughts, anxiety, hallucinations, confusion, depression, thoughts of **self-harm** or **suicide**. This can happen to people who have never had mental health problems before. These can occur within the first month of treatment with PLAQUENIL.

When you go outside, protect your skin from the sun by:
- wearing appropriate clothing, and
- using sunscreen cream with a minimum SPF 30 rating.

It is unclear whether PLAQUENIL may affect male fertility. Talk to your doctor if you would like to father a child in the future.

Driving and Using Machines: You may have blurry vision when taking PLAQUENIL. Do not drive or do things that require you to be alert. Wait until you know how you respond to PLAQUENIL and can see well. If you continue to have difficulty, your doctor may reduce your dose.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PLAQUENIL:

- Drugs for depression (tricyclic antidepressants) and psychiatric disorders (antipsychotics).
- Digoxin. If you are taking both PLAQUENIL and digoxin, your doctor may decide to check the level of digoxin in your blood, as the dose may need to be reduced.
- Anti-diabetic drugs, including insulin. If you take PLAQUENIL and a drug for diabetes or high blood sugar, there is a risk of having very low blood sugar. This can be life-threatening. Your doctor may decide to reduce the doses of the drug or insulin to control diabetes.
- Antiepileptic drugs (e.g. carbamazepine).
- Some antibiotics used for infections (e.g. aminoglycoside antibiotics, erythromycin).
- Neostigmine and pyridostigmine (medicines used to treat muscle disorders).
- Cimetidine (medicine used to treat heartburn).
- Cyclosporine (an immunosuppressant medication).
- Drugs known as CYP2C8 and CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir, gemfibrozil, ritonavir, clarithromycin).
- Drugs known as CYP2C8 and CYP3A4 inducers (e.g. rifampin, St. John's Wort, carbamazepine, phenobarbital).

- Medicines that are known to cause cardiac arrhythmias (irregular heartbeats).
- Halofantrine (a medicine used to treat malaria). If you are taking halofantrine, you should not be taking PLAQUENIL at the same time.
- Antacids. You should take antacids at least 2 hours before or 2 hours after taking PLAQUENIL.
- Rabies vaccine.
- Medicines that may affect the liver, the kidney, the skin or the eye.
- Medicines that may increase the risk of convulsions (e.g. antimalarials (mefloquine)).
- Medicines that decrease blood salt levels (e.g. water pills, laxatives, amphotericin B, high dose corticosteroids, and proton pump inhibitors).
- Agalsidase (a medicine used to treat a rare genetic disease called Fabry disease).
- Medicines that may increase risk of retinal toxicity. An example is tamoxifen, which is used to treat breast cancer. When taken alone, both PLAQUENIL and tamoxifen can cause damage to your retina at in the eye. Taking both drugs at the same time can increase your risk of retinal damage.
- Praziquantel (a medicine used to treat some infestations).

Do NOT eat grapefruit or drink grapefruit juice while taking PLAQUENIL.

PLAQUENIL has been used safely with salicylates (Aspirin®), non-steroidal anti-inflammatory medications, methotrexate and corticosteroids.

How to take PLAQUENIL:

Take PLAQUENIL exactly as your doctor told you to. Never take more PLAQUENIL than your doctor has prescribed.

To help avoid an upset stomach, take PLAQUENIL with a meal or a glass of milk.

Usual dose:

Your doctor will decide on the best dose for you. It may be based on your weight, physical health and other factors such as what other medications you are taking. The dose may need to be stopped or temporarily reduced due to side effects. The dose may then be re-started or increased to an optimum level by your doctor. Your dose will likely be lowered during treatment, after your Initial Dose. You may take the lower dose for a lengthy amount of time. This is called a Maintenance Dose.

Condition	Recommended dose		Number of tablets a day
Rheumatoid Arthritis	Initial:	400 – 600 mg a day	2 - 3
	Maintenance:	200 – 400 mg a day	1 - 2
Lupus Erythematosus	Initial:	400 mg, once or twice a day	2 - 4
	Maintenance:	200 – 400 mg a day	1 - 2
Malaria (adults)	Prevention:	400 mg a week, on the same day of each week, starting 2 weeks before exposure.	2
	Treatment:	800 mg initially, followed by 400 mg 6-8 hours later, and then 400 mg daily for the next two days.	4 2 2
Malaria (children)	Your dose will be calculated by your doctor based on each child's body weight.		

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

For patients with RA, SLE or DLE, if PLAQUENIL makes your symptoms completely better, talk to your doctor. They may want to bring down your daily dose. Never change your dose without talking with your doctor first.

Overdose:

Taking too much PLAQUENIL is dangerous and can lead to death. You could have symptoms of overdose within 30 minutes after taking it.

Taking too much PLAQUENIL is also dangerous for children. Children have died by taking too much PLAQUENIL. 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.

Symptoms of overdose include:

- headache

- feeling drowsy
- vision problems, such as blurry or double vision
- heart problems, such as uneven heartbeats or rapid heartbeats
- fainting
- muscle weakness
- convulsions
- serious trouble breathing

If you think you, or a person you are caring for, have taken too much PLAQUENIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using PLAQUENIL?

These are not all the possible side effects you may feel when taking PLAQUENIL. If you experience any side effects not listed here, contact your healthcare professional.

Before and during your treatment with PLAQUENIL your doctor may do some tests. These may include:

- blood tests
- an electrocardiogram (ECG)
- a periodic exam of your muscles and tendon reflexes
- complete eye exams

PLAQUENIL can cause permanent **eye damage**. To help prevent this, you should have an eye exam before you start taking PLAQUENIL. You will need more eye exams while you are taking PLAQUENIL.

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			

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	
Nausea, stomach pain, stomach cramps	✓		
COMMON			
Diarrhea		✓	
Vomiting		✓	
Anorexia: loss or lack of appetite		✓	
Visual problems and damage to the retina of the eye: blurred vision, seeing halos around lights, especially at night. Seeing light flashes and streaks. Night blindness with difficulty seeing at night or in poor light. Visual field loss including blind spots or blind areas in your vision. Change in eye colour. Difficulty focusing your eyes, or skipping words when reading.		✓	
Headache	✓		
Rash, itchy rash with raised red bumps		✓	
Nervousness, quick changes in mood (emotional lability)		✓	
RARE			
Dizziness or vertigo: feel as if you or the objects around you are moving when they are not.	✓		
Change in colour of skin, mucous membranes and hair: bleaching of hair. Loss or increase in skin pigment (bluish-black colour).		✓	
Alopecia: hair loss from your head or any part of your body.		✓	

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	
Hearing problems: ringing in the ears. Hearing loss.		✓	
Nerve and muscle problems: tingling, numbness, burning pain, weakness, cramps, spasms, restlessness, rigidity, tremors, twitches, difficulty walking		✓	
UNKNOWN FREQUENCY			
Allergic reaction or angioedema: rash, hives, swelling of the face, lops, tongue or throat, difficulty swallowing or breathing			✓
Heart rhythm disorders including long QT interval, torsade de pointes and heart block: abnormal heartbeat, life-threatening irregular heartbeat, palpitations			✓
Severe, life-threatening skin problems including Toxic Epidermal Necrolysis, Erythema Multiforme, Stevens-Johnson syndrome, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome): rash, red skin, red or purple skin patches possibly with blister or crust in the center. Pus filled rash. Peeling skin, blisters on lips, eyes, skin or in the mouth. Itching or burning. Flu-like fever.			✓
Severe breathing problems including bronchospasm, angioedema: sudden shortness of breath			✓
Increased sensitivity to sunlight. Skin rash due to sunlight can be reduced by appropriate use of sunscreen creams.		✓	
Muscle weakness		✓	
Permanent damage to vision		✓	

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	
Fainting spells or loss of consciousness		✓	
Heart problems or heart failure, cardiomyopathy, an enlarged or weak heart: shortness of breath with exercise or even at rest. Swelling of the legs, ankles and feet. Irregular heartbeats that feel rapid or pounding. Chest pain. Sudden fainting or feeling tired, light-headed and dizzy. You can have a seizure or fit.			✓
Liver problems: unusual tiredness, nausea, vomiting, abdominal pain, jaundice (yellow discoloration of the eyes or skin), dark urine		✓	
Bone Marrow Depression or a decrease in production of cells: Low White Blood cells (leukocytes): Fever and chills. Infections. Anemia or low red blood cells (erythrocytes): Fatigue, extreme tiredness that does not get better with rest. Paleness of skin, lips, and nail beds. Low platelets used for blood clotting (thrombocytes): Bleeding: nose bleeds, gums, or mouth. Tiny red spots on the skin.		✓	
Convulsions, seizures or fits			✓
Psychosis: hallucinations, loss of contact with reality		✓	

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	
Mental health problems: irrational/abnormal thoughts, irritability, anxiety, hallucinations, feeling confused or depressed, agitation, difficulty sleeping, delusions (feelings of distrust and false beliefs), changes in mood, feeling elated or overexcited or abnormally happy		✓	
Thoughts or actions of **suicide** or **self-harm**			✓
Hypoglycemia or low blood sugar: hunger pains, sweating, shakiness, weakness, dizziness, fast heartbeat, nausea, irritability, blurred vision, confusion, loss of consciousness		✓	
Muscle, nerve and tendon problems: long-lasting involuntary muscle contraction, impairment of voluntary movements, tremor. Weakness. Decreased reflexes or feeling by nerves.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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/adverse-reaction-reporting.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.

Storage:

- Keep out of reach and sight of infants and small children.
- Store at room temperature (15°C - 30°C).
- Do not use PLAQUENIL after the expiry date.

If you want more information about PLAQUENIL:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.sanofi.ca) or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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