PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr MINT-HYDROXYCHLOROQUINE

Hydroxychloroquine Sulfate Tablets

Tablets, 200 mg, Oral

USP

Anti-Inflammatory – Antimalarial – Aminoquinolines

Mint Pharmaceuticals Inc.
6575 Davand Drive Mississauga,
Ontario
L5T 2M3

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RECENT MAJOR LABEL CHANGES

7 Warning and Precautions, Cardiovascular	08/2023
7 Warnings and Precautions, Hepatic/Biliary/Pancreatic	07/2024
7 Warnings and Precautions, Musculoskeletal	07/2024
7 Warnings and Precautions, Renal	07/2024
7 Warnings and Precautions, 7.1.1 Pregnant Women	07/2024
7 Warnings and Precautions, Reactivation of Infections	02/2025

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MINT-HYDROXYCHLOROQUINE (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.* MINT-HYDROXYCHLOROQUINE 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. MINT-HYDROXYCHLOROQUINE 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,* MINT-HYDROXYCHLOROQUINE 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): MINT-HYDROXYCHLOROQUINE is contraindicated in children below 6 years of age (see 2 CONTRAINDICATIONS). The safety of hydroxychloroquine sulfate tablets 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 hydroxychloroquine sulfate tablets 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 hydroxychloroquine sulfate tablets did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients. MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE 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 this population (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

MINT-HYDROXYCHLOROQUINE 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).

- MINT-HYDROXYCHLOROQUINE 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. MINT-HYDROXYCHLOROQUINE 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: MINT-HYDROXYCHLOROQUINE 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: MINT-HYDROXYCHLOROQUINE 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: MINT-HYDROXYCHLOROQUINE 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: MINT-HYDROXYCHLOROQUINE 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 fivetimes 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	Colloidal silicon dioxide, dibasic calcium phosphate, hypromellose, macrogol, magnesium stearate, polysorbate, polyvinyl alcohol, pregelatinized starch, titanium dioxide, talc.

Description

MINT-HYDROXYCHLOROQUINE is available as: white to off-white, capsule shaped tablets debossed with HCQS on one side and plain on the reverse side, containing 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base), bottles of 100 and 500.

7 WARNINGS AND PRECAUTIONS

General

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

Malaria

MINT-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 (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 hydroxychloroquine sulfate tablets. In multiple cases, endomyocardial biopsy showed association of the cardiomyopathy with phospholipidosis in the absence of inflammation, infiltration, or necrosis. Drug-induced phospholipidosis may occur in other organ systems. **MINT-HYDROXYCHLOROQUINE 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). Monitor cardiac function as clinically indicated during therapy. Discontinue MINT-

HYDROXYCHLOROQUINE if cardiotoxicity is suspected or demonstrated by tissue biopsy.

Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias
MINT-HYDROXYCHLOROQUINE 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 hydroxychloroquine sulfate tablets 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 MINT-HYDROXYCHLOROQUINE in patients who develop torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. If cardiac complications due to MINT-HYDROXYCHLOROQUINE are suspected, treatment should be discontinued.**

MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE 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).

Carefully consider the benefits and risks before prescribing azithromycin or other macrolide antibiotics for any patients taking MINT-HYDROXYCHLOROQUINE, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see 9 DRUG INTERACTIONS).

The magnitude of QT, PR or QRS prolongation with MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE 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

Hydroxychloroquine sulfate tablets 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 MINT-HYDROXYCHLOROQUINE should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with MINT-HYDROXYCHLOROQUINE should have their blood glucose level checked and the need for MINT-HYDROXYCHLOROQUINE treatment reviewed as necessary. In cases of severe hypoglycemia, MINT-HYDROXYCHLOROQUINE should be discontinued and alternative therapy should be considered. If patients use MINT-HYDROXYCHLOROQUINE concomitantly with antidiabetic drugs, a decrease in doses of insulin or antidiabetic drugs may be required as MINT-HYDROXYCHLOROQUINE 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

MINT-HYDROXYCHLOROQUINE 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 (4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations, 8.2 Clinical Trial Adverse Reactions, Hepatobiliary disorders, 8.5 Post-Market Adverse Reactions and 9 DRUG INTERACTIONS).

Use of MINT-HYDROXYCHLOROQUINE 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).

Hepatotoxicity

Serious cases of drug-induced liver injury (DILI) including hepatocellular injury, cholestasis acute hepatitis and fulminant hepatic failure (including fatal cases) have been reported during use of MINT-HYDROXYCHLOROQUINE. Some of the cases could be associated with risk factors that include pre- existing liver disease (e.g., hepatobiliary disorders, acute viral hepatitis), or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or, concomitant hepatotoxic medications.

Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, and repeated as clinically indicated.

For patients with significant liver function abnormalities (see 8 ADVERSE REACTIONS), Healthcare professionals should assess the benefits/risk of continuing the treatment. If active liver diseases or unexplained transaminases elevations develop during therapy, MINT-HYDROXYCHLOROQUINE should be discontinued.

Immune

Reactivation of Infections

Based on limited data, the reactivation of hepatitis B virus, herpes zoster virus and tuberculosis has been reported in patients treated with hydroxychloroquine administered alone or more often in combination with other immunosuppressants. Consider the risk of reactivation prior to using hydroxychloroquine in patients with previous history of these infections.

Monitoring and Laboratory Tests

ECG assessments are recommended at baseline and periodically during treatment with MINT-HYDROXYCHLOROQUINE. More frequent monitoring is recommended if MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE (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).

Aggravation of Myasthenia Gravis

Aggravation of symptoms of myasthenia gravis (i.e., weakness of the skeletal muscles, shortness of breath, dysphagia, diplopia etc.) have been reported in myasthenic patients receiving hydroxychloroquine therapy.

Skeletal Muscle Myopathy or Neuropathy

Muscle and nerve biopsies have shown associated phospholipidosis. Drug-induced phospholipidosis may occur in other organ systems. Monitor muscle strength and deep tendon reflexes during therapy.

Discontinue MINT-HYDROXYCHLOROQUINE if muscle or nerve toxicity is suspected or demonstrated by tissue biopsy.

Neurologic
Extrapyramidal reactions have been reported in patients taking hydroxychloroquine sulfate tablets (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 MINT-HYDROXYCHLOROQUINE with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

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

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

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

MINT-HYDROXYCHLOROQUINE 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).

Proteinuria with or without moderate reduction in glomerular filtration rate have been reported with the use of MINT-HYDROXYCHLOROQUINE. Renal biopsy showed phospholipidosis without immune deposits, inflammation, and/or increased cellularity. Healthcare professionals should consider phospholipidosis as a possible cause of renal injury in patients with underlying connective tissue disorders who are receiving MINT-HYDROXYCHLOROQUINE. Drug-induced phospholipidosis may occur in other organ systems. Discontinue MINT-HYDROXYCHLOROQUINE if renal toxicity is suspected or demonstrated by tissue biopsy.

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

Severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse drug reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with hydroxychloroquine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Monitor for serious skin reactions, especially in patients receiving a drug that may also induce dermatitis. If signs and symptoms suggestive of severe skin reactions appear in any patients, hydroxychloroquine should be withdrawn at once and alternative therapy should be considered.

Worsening of Psoriasis and Porphyria

MINT-HYDROXYCHLOROQUINE may cause acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although MINT-HYDROXYCHLOROQUINE may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. MINT-HYDROXYCHLOROQUINE is not recommended for the treatment of psoriasis or porphyria as these conditions may be exacerbated by its use. Use caution in patients with psoriasis. Outcome is usually favorable after discontinuation of drug.

Patients with porphyria cutanea tarda (PCT) are more susceptible to hepatotoxicity.

7.1 Special Populations

7.1.1 Pregnant Women

MINT-HYDROXYCHLOROQUINE 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 for auto-immune diseases: data from a population-based cohort study (Huybrechts et al. 2021) including 2045 hydroxychloroquine exposed pregnancies suggests a small increased risk of major congenital malformations associated with hydroxychloroquine exposure in the first trimester of pregnancy (n = 112 events). The adjusted relative risk (RR) was 1.26 (95% confidence interval, 1.04-1.54).

Close monitoring of pregnancy is recommended for early detection of congenital malformations. 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 MINT-HYDROXYCHLOROQUINE 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 hydroxychloroquine sulfate tablets 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).

MINT-HYDROXYCHLOROQUINE 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 hydroxychloroquine sulfate tablets (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).

MINT-HYDROXYCHLOROQUINE 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.

Renal and urinary disorders
Not known: Renal Phospholipidosis leading to renal injury (see 7 WARNINGS AND PRECAUTIONS, Renal).

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: Erythema multiforme, photosensitivity, exfoliative dermatitis, urticarial,

morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Sweet's syndrome and severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) (see 7 WARNINGS AND PRECAUTIONS, Skin).

8.5 Post-Market Adverse Reactions

The frequency of post-market adverse reactions cannot be estimated from available data.

Psychiatric disorders
Depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.

Hepatobiliary disorders
Not known: Drug-induced liver injury (DILI) including hepatocellular injury and acute hepatitis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drugs that Prolong the PR, QRS and/or QTc Intervals
MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE 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.

Macrolide antibiotics
Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risks should also be undertaken before prescribing other macrolide antibiotics for any patients taking hydroxychloroquine because of the potential for a similar risk when hydroxychloroquine is co-administered with these medicines.

Halofantrine should not be administered with MINT-HYDROXYCHLOROQUINE.

Drugs that Affect Electrolytes
Caution is recommended if MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE is included below. This list of possible drug interactions is not exhaustive. MINT-HYDROXYCHLOROQUINE 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).

Pharmacokinetic interaction

In vitro, hydroxychloroquine is metabolized by CYP2C8, CYP3A4 and CYP2D6, as well as by FMO-1 and MAO-A, with no major involvement of a single CYP or enzyme (see 10 CLINICAL PHARMACOLOGY). Therefore, inhibitors and inducers of CYP2C8 and CYP3A4 may affect hydroxychloroquine exposure.

Hydroxychloroquine inhibits CYP2D6 in vivo. In vitro, hydroxychloroquine inhibits CYP3A4/5, CYP2D6, OCT1, OCT2, MATE1, MATE2-K, is a weak inhibitor of P-glycoproteins (P-gp) and basic model calculations for these predicts the risk of in vivo interaction. Therefore co-administration of hydroxychloroquine with drugs that are primarily metabolized by CYP2D6 and CYP3A4/5 and P-gp may result in increased plasma concentrations of such drugs which could increase or prolong their therapeutic effect and adverse events (see Table 1). For substrates of OCT1, OCT2, MATE1, MATE2-K, there is insufficient data to rule out an in vivo effect.

Based on in vitro data, hydroxychloroquine does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 (IC50 > 200µM) and the transporters OATP1B1, OATP1B3, OAT1 and OAT3 (IC50 > 110µM). In vitro, hydroxychloroquine does not induce CYP1A2, CYP2B6 and CYP3A4 at non- cytotoxic concentrations up to 75µM.

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 MINT-HYDROXYCHLOROQUINE is co-administered with agalsidase.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Aminoglycoside antibiotics	T	↑ blocking action	MINT-HYDROXYCHLOROQUINE may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics.
Antacids (e.g. magnesium-containing antacids, kaolin)	T	↓ absorption of hydroxychloroquine	As with chloroquine, co-administration with antacids (such as magnesium-containing antacids or kaolin) may result in reduced absorption of MINT-HYDROXYCHLOROQUINE. Per extrapolation, MINT-HYDROXYCHLOROQUINE should therefore be administered at least two hours apart from antacids or kaolin.
Antidiabetic drugs and insulin	C	↑ effect of antidiabetic	As MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE.
Antimalarial drugs known to lower the convulsion threshold (e.g. mefloquine)	T	↑ risk of convulsions	MINT-HYDROXYCHLOROQUINE can lower the convulsive threshold. Co-administration of MINT-HYDROXYCHLOROQUINE 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.	C	↓ efficacy	Lack of efficacy of hydroxychloroquine sulfate tablets was reported when rifampin, a CYP2C8 and CYP3A4 strong

Proper/Common name	Source of Evidence	Effect	Clinical comment
John's Wort, carbamazepine, phenobarbital)			inducer, was concomitantly administered. PBPK simulations based on in vitro data support this observation, as strong CYP2C8 and/or CYP3A4 inducers showed a decrease in hydroxychloroquine exposure. 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 hydroxychloroquine	Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for hydroxychloroquine sulfate tablets. PBPK simulations based on in vitro data show that strong CYP2C8 or CYP3A4 inhibitors would increase hydroxychloroquine exposure. Co-administration of MINT-HYDROXYCHLOROQUINE with strong CYP2C8 and/or CYP3A4 inhibitors (such as, but not limited to, ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir) may result in increased plasma concentrations of hydroxychloroquine. In the absence of in vivo drug interaction

Proper/Common name	Source of Evidence	Effect	Clinical comment
			studies, caution is advised (e.g. monitoring for adverse reactions).
CYP3A4 substrates (e.g. midazolam, simvastatin, cyclosporine, statins)	C	↑ exposure of drugs highly metabolized by CYP3A4	Hydroxychloroquine inhibits CYP3A4 in vitro. An increased plasma level of cyclosporine (a CYP3A4 and p-gp substrate) was reported when cyclosporine and hydroxychloroquine were coadministered. PBPK simulations based on in vitro data support this observation as hydroxychloroquine increased the exposure of midazolam and simvastatin. Caution is advised (e.g. monitoring for adverse reactions) when CYP3A4 substrates (such as cyclosporine, statins) are concomitantly administered.
CYP2D6 substrates (e.g. metoprolol, flecainide, propafenone)	CT	↑ exposure of drugs metabolized by CYP2D6	Hydroxychloroquine inhibits CYP2D6 in vitro. In patients receiving hydroxychloroquine and a single dose of metoprolol, a CYP2D6 substrate, the Cmax and AUC of metoprolol were increased by 1.7-fold, which suggests that hydroxychloroquine is a weak inhibitor of CYP2D6. However, given that metoprolol is a moderate sensitive substrate, the maximum increase in exposure could result in levels considered consistent with a moderate or strong inhibitor when co- administered with a sensitive substrate. Caution is advised (e.g. monitoring of adverse reactions or for plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (such as flecainide,

Proper/Common name	Source of Evidence	Effect	Clinical comment
			propafenone) are concomitantly administered.
Drugs that induce retinal toxicity (e.g. tamoxifen)	C	↑ risk of retinopathy	An increased risk of toxic retinopathy was reported when Hydroxychloroquine was used concurrently with tamoxifen citrate. Concomitant use of Hydroxychloroquine 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 (e.g. macrolides including azithromycin), domperidone, 5-hydroxytryptamine (5-HT)3 receptor antagonists, kinase inhibitors, histone deacetylase inhibitors beta-2 adrenoceptor agonists)	C	↑ risk of arrhythmia	Hydroxychloroquine 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 Hydroxychloroquine 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 (e.g. macrolides including azithromycin); 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 Hydroxychloroquine 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	MINT-HYDROXYCHLOROQUINE may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including antagonism of effect of neostigmine .
P-glycoprotein (P-gp) substrates (e.g. cyclosporine, digoxin, dabigatran)	C	↑ plasma/ serum levels	In vitro, hydroxychloroquine inhibits P-gp at high concentrations. Therefore, there is a potential for increased concentrations of P-gp substrates when Hydroxychloroquine is concomitantly administered. Increased plasma cyclosporine levels were reported when cyclosporine and Hydroxychloroquine were co-administered. Increased digoxin serum levels were reported when digoxin and Hydroxychloroquine 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)

Proper/Common name	Source of Evidence	Effect	Clinical comment
			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 Hydroxychloroquine.
Pyridostigmine	T	↓ effect	Hydroxychloroquine may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including antagonism of effect of pyridostigmine.
Select anion/cation transporter substrates, including substrates of: OCT1, OCT2, MATE1 and MATE2-K (e.g metformin)	T	↑ exposure of drugs which are substrates of **:** OCT1, OCT2, MATE1 and MATE2-K	Hydroxychloroquine inhibits OCT1, OCT2, MATE1, MATE2-K *in vitro* and the risk of an in vivo interaction cannot be ruled out.
Vaccine: Human diploid cell rabies vaccine	T	↓ antibody response	MINT-HYDROXYCHLOROQUINE may also be subject to several of the known interactions of chloroquine, even though specific reports have not appeared, including reduction of the antibody response to primary immunization with intradermal human diploid cell rabies vaccine.

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 MINT-HYDROXYCHLOROQUINE.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

MINT-HYDROXYCHLOROQUINE belongs to the 4-aminoquinoline class. Hydroxychloroquine sulfate tablets have 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 plasma or blood concentrations is achieved in approximately 3 to 4 hours. Mean absolute oral bioavailability is 79% (SD: 12%) in fasting conditions.

Distribution:
Hydroxychloroquine has a large volume of distribution (5500 L when assessed from blood concentrations, 44 000 L when assessed from plasma concentrations), due to extensive tissue accumulation such as eyes, kidney, liver and lungs) 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. *In vitro*, hydroxychloroquine is metabolized mainly by CYP2C8, CYP3A4 and CYP2D6 as well as by FMO-1, and MAO-A, with no major involvement of a single CYP or enzyme.

Elimination:
Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 (SD:9) to 50 (SD:16) days. The hydroxychloroquine dose eliminated as unchanged drug in urine is reported to range from 18% to 27%. After chronic repeated oral administration of 200 mg and 400 mg hydroxychloroquine sulfate once a day in adult patients with lupus or rheumatoid arthritis, the average steady-state blood concentrations were around 450-490 ng/mL and 870-970 ng/mL, respectively, with large inter-individual variability in concentration.

The pharmacokinetics of hydroxychloroquine appears to be linear in the therapeutic dose range of 200 to 400 mg/day.

Renal impairment
A formal study assessing the pharmacokinetics in patients with impaired renal function has not been conducted. In studies limited by the number of participants and with differently combined

patients groups, hydroxychloroquine levels were assessed in patients with SLE with different stages of renal impairment. When compared to patients with normal renal function, hydroxychloroquine exposure was increased up to 46% in patients with moderate and severe renal impairment. A reduction in dosage may be necessary in patients with renal impairment (see 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations and see 7 WARNINGS AND PRECAUTIONS, Renal)

Hepatic impairment
The effect of hepatic impairment on hydroxychloroquine pharmacokinetics has not been evaluated in a specific PK study. (see 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations and 7 WARNINGS AND PRECAUTIONS, Hepatic).

Geriatric
There is insufficient clinical data to inform on hydroxychloroquine pharmacokinetics in geriatric patients.

Pediatrics
The pharmacokinetics of hydroxychloroquine in children below 18 years of age have not been established.

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

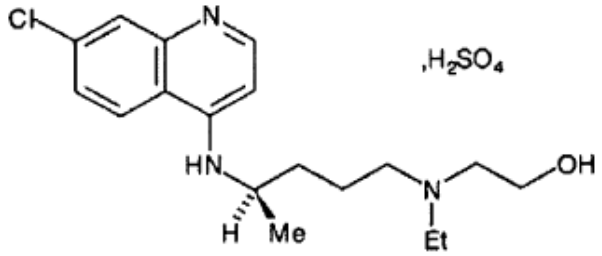
Chemical name: Ethanol, 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethyl]amino-, (±), sulfate (1:1) (salt)

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

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

Molecular mass: 434.0 g/mol

Structural formula:



and enantiomer

Physiochemical properties: White or practically white, crystalline powder, odourless and has a bitter taste. Solubility: Freely soluble in water, practically insoluble in alcohol, in chloroform, and in ether. Melting range: 238-242°C.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A double blind, randomized, two-treatment, single-period, parallel, single-dose, comparative oral bioavailability study of Mint-Hydroxychloroquine (hydroxychloroquine sulfate) 200 mg tablets (Mint Pharmaceuticals Inc.) and PLAQUENIL® (hydroxychloroquine sulfate) 200 mg tablets (Sanofi- Aventis Canada Inc.) was conducted in 111 healthy adult male subjects under fasting conditions. The results for the study are tabulated below.

Summary table of the comparative bioavailability data

Hydroxychloroquine Sulfate (1 x 200 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{0\,72}$ (hr. ng/mL)	5301.4 5507.3 (28.6)	5193.6 5388.8 (294.4)	102.1	93.7-111.2
C_{max} (ng/mL)	255.1 266.1 (31.8)	253.4 266.4 (35.5)	100.7	91.7-110.5
T_{max}[3] (h)	4.5 (2.0-6.5)	4.5 (1.5-7.0)		

[1] MINT-HYDROXYCHLOROQUINE (hydroxychloroquine sulfate) 200 mg tablets, Mint-Pharmaceuticals Inc., Canada.
[2] PLAQUENIL® (hydroxychloroquine sulfate) 200 mg tablets, sanofi-aventis Canada Inc., Canada, were purchased in Canada.
[3] Expressed as the median (range) only.

Note: AUC_I and $T_{1/2}$ are not reported; these parameters could not be reliably estimated due to the long half- life of hydroxychloroquine sulfate and the design of the study.

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PLAQUENIL tablets, 200 mg, submission control 287053, Product Monograph, sanofi-aventis Canada Inc. (FEB 21, 2025)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr MINT-HYDROXYCHLOROQUINE

Hydroxychloroquine Sulfate Tablets

Read this carefully before you start taking **MINT-HYDROXYCHLOROQUINE** 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 **MINT-HYDROXYCHLOROQUINE**.

What is MINT-HYDROXYCHLOROQUINE used for?
MINT-HYDROXYCHLOROQUINE 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.

MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE with a healthcare professional's prescription.

How does MINT-HYDROXYCHLOROQUINE work?
It is not known how MINT-HYDROXYCHLOROQUINE works in the body to treat RA, SLE, and DLE. MINT-HYDROXYCHLOROQUINE may take up to six months to take effect. For malaria, MINT-HYDROXYCHLOROQUINE works by killing the parasite that causes the infection.

What are the ingredients in MINT-HYDROXYCHLOROQUINE?
Medicinal ingredient: hydroxychloroquine sulfate.
Each 200 mg tablet contains 155 mg of hydroxychloroquine as the base.

Non-medicinal ingredients: colloidal silicon dioxide, dibasic calcium phosphate, hypromellose, macrogol, magnesium stearate, polysorbate, polyvinyl alcohol, pregelatinized starch, titanium dioxide, talc.

MINT-HYDROXYCHLOROQUINE comes in the following dosage forms:
Tablets, 200 mg.

Do not use MINT-HYDROXYCHLOROQUINE if:

- you are allergic to
    - hydroxychloroquine sulfate
    - any of the other ingredients of MINT-HYDROXYCHLOROQUINE
    - any similar drugs such as chloroquine
- you have retinopathy. This is an eye problem affecting the retina at the back of your eye. MINT-HYDROXYCHLOROQUINE may cause irreversible damage to your retina. You should tell your healthcare professional 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 MINT-HYDROXYCHLOROQUINE. 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. MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE.
    - 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, think you may be pregnant or you are planning to get pregnant.

    - MINT-HYDROXYCHLOROQUINE may be passed to your unborn baby. MINT-HYDROXYCHLOROQUINE may harm your unborn baby and cause birth defects. Your healthcare professional will assess the benefit and risk of using MINT-HYDROXYCHLOROQUINE during pregnancy.

- are breastfeeding. MINT-HYDROXYCHLOROQUINE passes into breast milk in small amounts.
    - Infants can be very sensitive to the toxic effects of drugs like MINT-HYDROXYCHLOROQUINE. There is not enough MINT-HYDROXYCHLOROQUINE in breast milk to protect an infant against malaria. The infant should receive their own malaria treatment if necessary.
    - MINT-HYDROXYCHLOROQUINE should not be used during breast-feeding unless your healthcare professional considers the benefits outweigh the risks.
    - Talk to your healthcare professional about the risks MINT-HYDROXYCHLOROQUINE can have on your baby. These risks depend on:
        - why you are taking MINT-HYDROXYCHLOROQUINE;
        - how long you will be taking MINT-HYDROXYCHLOROQUINE for.

- have diabetes or symptoms of **low blood sugar**. MINT-HYDROXYCHLOROQUINE 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 an inactive chronic infection such as hepatitis B, chickenpox, shingles or tuberculosis. These infections may flare up .

- have alcoholism.

- have a blood disease, including a rare blood disease called porphyria. MINT-HYDROXYCHLOROQUINE can make this worse.

- have skin problems or diseases such as psoriasis MINT-HYDROXYCHLOROQUINE can make these worse.

- 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-phosphatedehydrogenase 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 MINT-HYDROXYCHLOROQUINE.

- have or have had myasthenia gravis (a disease that causes muscle weakness and fatigue). Your symptoms such as muscle weakness, shortness of breath, difficulty in swallowing or double vision might get worse.

Other warnings you should know about:
MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE for long periods of time. These are serious and can result in death. Your healthcare professional will check your heart regularly.

MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE.

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

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

Muscle, nerve and tendon problems: MINT-HYDROXYCHLOROQUINE may cause muscle and nerve problems. Caution should be taken when you take this medicine for a long time. Your healthcare professional will check for muscle weakness, numbness and pain.

Liver problems: MINT-HYDROXYCHLOROQUINE may cause liver problems, including liver failure, which can cause death. MINT-HYDROXYCHLOROQUINE may also cause hepatitis B to reactivate. Your healthcare professional will do tests to check your liver health.

Kidney problems: MINT-HYDROXYCHLOROQUINE may cause kidney problems. Kidney problems can also be caused by the build up of phospholipids (a type of fat).

Severe Skin Reactions / Rashes: MINT-HYDROXYCHLOROQUINE can cause **severe cutaneous adverse drug reactions (SCARs)** such as drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and maybe fatal. These skin reactions and rashes can involve ulcers of the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). Flu-like symptoms such as fever, headache and body ache can happen before these reactions start. The skin reactions and rashes may progress to blisters and peeling skin. If you develop these symptoms, stop taking MINT-HYDROXYCHLOROQUINE and tell your healthcare professional right away.

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

Fertility (males): It is unclear whether MINT-HYDROXYCHLOROQUINE may affect male fertility. Talk to your healthcare professional if you would like to father a child in the future.

Check-ups and testing:
Before and during your treatment with MINT-HYDROXYCHLOROQUINE your healthcare professional may do some tests. These may include:

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

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 MINT-HYDROXYCHLOROQUINE:

- Drugs for depression (tricyclic antidepressants) and psychiatric disorders (antipsychotics).
- Digoxin. If you are taking both MINT-HYDROXYCHLOROQUINE and digoxin, your healthcare professional may decide to check the level of digoxin in your blood, as the dose may need to be reduced.
- Anti-diabetic drugs, including insulin and metformin. If you take MINT-HYDROXYCHLOROQUINE 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 healthcare professional may decide to reduce the doses of the drug or insulin to control diabetes.
- Antiepileptic drugs (e.g. carbamazepine).

- Some antibiotics used for bacterial infections (e.g. aminoglycoside antibiotics, erythromycin, azithromycin, moxifloxacin, clarithromycin, spiramycin). Taking these antibiotics at the same time as hydroxychloroquine may increase the chance of you getting side effects that affect your heart which could be life -threatening.
- 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
    - Medicines used to treat fungal infections like ketoconazole, itraconazole, fluconazole
    - Medicines used to treat infections like erythromycin, clarithromycin.
    - Medicines used to treat nausea and vomiting like aprepitant
    - Medicines used to treat multiple sclerosis like teriflunomide,.
    - Medicines used to treat viral infections in immunocompromised patients like letermovir, ritonavir.
- Drugs known as CYP2C8 and CYP3A4 inducers
    - Medicines used to treat epilepsy like carbamazepine, phenobarbital.
    - Medicines used to treat Tuberculosis like rifampin.
    - Medicine used to treat depression like St. John's Wort.
- Medicines that are known to cause cardiac arrhythmias (irregular heartbeats).
- Medicines used to treat heart problems like digoxin, flecainide, propafenone
- Medicines used to treat high blood pressure like metoprolol
- Medicines used to treat blood clots like dabigatran, clopidogrel
- Medicines used to treat blood lipid problems, like statins (e.g. simvastatin), or gemfibrozil
- Medicines used for sedation, like midazolam
- Halofantrine (a medicine used to treat malaria). If you are taking halofantrine, you should not be taking MINT-HYDROXYCHLOROQUINE at the same time.
- Antacids. You should take antacids at least 2 hours before or 2 hours after taking MINT-HYDROXYCHLOROQUINE.
- 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 MINT-HYDROXYCHLOROQUINE 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 MINT-HYDROXYCHLOROQUINE.

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

How to take MINT-HYDROXYCHLOROQUINE:
Take MINT-HYDROXYCHLOROQUINE exactly as your healthcare professional told you to. Never take more MINT-HYDROXYCHLOROQUINE than your healthcare professional has prescribed.

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

Usual dose:
Your healthcare professional 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 healthcare professional. 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 healthcare professional based on each child's body weight.	

Should you have a serious change of health at any point while taking MINT-HYDROXYCHLOROQUINE, see your healthcare professional.

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

Overdose:

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

Taking too much MINT-HYDROXYCHLOROQUINE is also dangerous for children. Children have died by taking too much hydroxychloroquine sulfate tablets. 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.

The symptoms of overdose can also be side effects of MINT-HYDROXYCHLOROQUINE. These 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 MINT-HYDROXYCHLOROQUINE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) 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 MINT-HYDROXYCHLOROQUINE?

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Nausea, stomach pain, stomach cramps	✓		
COMMON			
Diarrhea		✓	
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.		✓	
Hearing problems: ringing in the ears. Hearing loss.		✓	

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	
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 skin reactions such as: • **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** rash with a fever and flu-like symptoms and enlarged lymph nodes. • **Acute Generalized Exanthematous Pustulosis (AGEP):** blistering, widespread scaly skin, pus-filled spots together with fever. • **Stevens-Johnson syndrome (SJS):** blistering or peeling of the skin around the lips, eyes, mouth, nose, genitals, hands or feet, flu-like symptoms and fever. • **Toxic Epidermal Necrolysis (TEN):** multiple skin lesions, itching of the skin, joint aches, fever and a general ill feeling. • **Sweet's syndrome:** skin reaction including reddish-purple color, raised, painful sores, particularly			✓

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	
on your arms, hands, fingers, face and neck, fever. • **Erythema Multiforme**: skin reaction/rash characterised by raised red or purple skin patches, possibly with blister or crust in the centre with or without mild itching, joint pain, fatigue and 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		✓	
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, weakness, poor appetite.		✓	
Reactivation of chronic infections like herpes zoster, tuberculosis, hepatitis B, (when a previous infection becomes active again): rash		✓	

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	
that is painful, itchy or tingling, cough, fever, weight loss, joint pain and inflammation, fatigue, loss of appetite, nausea, yellowing of the skin or whites of eyes, abdominal pain			
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		✓	
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			✓

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	
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 MINT-HYDROXYCHLOROQUINE after the expiry date.

If you want more information about MINT-HYDROXYCHLOROQUINE:

- 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.mintpharma.com), or by calling 1-877-398-9696.

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