PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

MEFLOQUINE

Mefloquine Tablets

250 mg Mefloquine (as Mefloquine Hydrochloride)

ANTIMALARIAL AGENT

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Table of Contents

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250 mg Mefloquine (as Mefloquine Hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	250 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Prophylaxis
MEFLOQUINE (mefloquine hydrochloride) is indicated for the prophylaxis of *P. falciparum* and *P. vivax* malaria infections, including prophylaxis of chloroquine-resistant strains of *P. falciparum*.

Treatment of Acute Malaria Infections
MEFLOQUINE is indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible strains of *P. falciparum* (both chloroquine- susceptible and resistant strains) or by *P. vivax*.

CONTRAINDICATIONS

MEFLOQUINE (mefloquine hydrochloride) is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds, (e.g. quinine, quinidine, chloroquine) or to any components contained in the tablet.

Patients with active depression or a history of psychiatric disturbances (including depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders) or a

history of convulsions should not be prescribed MEFLOQUINE prophylactically since MEFLOQUINE may precipitate these conditions.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Mefloquine should not be prescribed for prophylaxis in patients with major psychiatric disorders (see **CONTRAINDICATIONS**).
- Mefloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued (see **WARNINGS – Neurologic)**.
- During prophylactic use, if psychiatric or neurologic symptoms occur, mefloquine should be discontinued and an alternative medication should be substituted (see **WARNINGS - Neurologic**)

General

- In case of life-threatening, serious or overwhelming malaria infections due to *P. falciparum*, patients should be treated with an intravenous antimalarial drug. Following completion of initial intravenous treatment, MEFLOQUINE may be given orally to complete the course of therapy.
- Patients with acute *P. vivax* malaria treated with MEFLOQUINE are at high risk of relapse because MEFLOQUINE does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse, after initial treatment of the acute infection with MEFLOQUINE, patients should subsequently be treated with an 8-aminoquinoline (e.g., primaquine).
- There are insufficient clinical data to document the effect of MEFLOQUINE in malaria caused by *P. ovale* or *P. malariae*.
- MEFLOQUINE has a long half-life; adverse reactions to MEFLOQUINE may occur or persist up to several weeks or months after discontinuation of the drug.
- In a small number of patients it has been reported that neuropsychiatric reactions (eg. depression, tinnitus, dizziness, vertigo or loss of balance) may continue for months or years after discontinuation of MEFLOQUINE, and permanent vestibular damage has been seen in some cases (see **ADVERSE REACTIONS**)

Cardiovascular

Caution should be exercised in prescribing MEFLOQUINE to patients suffering from cardiac conduction disorders. In patients with cardiac disease, the benefits of mefloquine therapy should be weighed against the possibility of adverse cardiac effects.

Parenteral studies in animals show that mefloquine, a myocardial depressant, possesses 20% of the anti-fibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of mefloquine on the compromised cardiovascular system has not been evaluated. However, transitory and clinically silent ECG alterations have been reported

during the use of mefloquine; alterations included sinus bradycardia, sinus arrhythmia, first degree AV-block, prolongation of the QTc interval and abnormal T waves.

Concomitant administration of MEFLOQUINE and other drugs known to alter cardiac conduction, including quinine, quinidine or chloroquine, may produce electrocardiographic abnormalities or cardiac arrest. If quinine or quinidine are to be used in the initial treatment of severe malaria, mefloquine administration should be delayed for at least 12 hours after the final dose of either of these drugs. (see DRUG INTERACTIONS)

Due to the risk of a potentially fatal prolongation of the QTc interval, halofantrine must not be given during MEFLOQUINE therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of MEFLOQUINE. The risk of QTc prolongation may also be expected if ketoconazole is taken during MEFLOQUINE therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of MEFLOQUINE, due to increased plasma concentrations and elimination half-life of mefloquine following co-administration with ketoconazole, (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Patients should be advised to consult a healthcare professional if they experience palpitations or any arrhythmia during chemoprophylaxis with mefloquine.

Hematologic

Cases of agranulocytosis and aplastic anemia have been reported (see **ADVERSE REACTIONS**).

In vitro and *in vivo* studies showed no hemolysis associated with glucose 6 phosphate dehydrogenase deficiency.

Hepatic

The pharmacokinetics of mefloquine in patients with compromised hepatic function have not been studied. Mefloquine is extensively metabolized in the liver by the cytochrome P450 system; in patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma levels.

Immune

Hypersensitivity reactions including anaphylaxis and pneumonitis have been associated with the use of mefloquine. As with most medications, hypersensitivity reactions, ranging from mild cutaneous events to anaphylaxis, cannot be predicted.

Neurologic/Psychiatric

Seizures:

In patients with epilepsy, mefloquine may increase the risk of convulsions. Therefore in these patients, MEFLOQUINE should be used only for treatment of acute malaria infections and only if there are compelling medical reasons.

Concomitant administration of mefloquine and anticonvulsants may reduce seizure control by lowering the plasma levels of the anticonvulsants. Patients taking anti-seizure medication concurrently with mefloquine should have blood levels of their anti-seizure medication monitored and the dosage adjusted as necessary. (See **DRUG INTERACTIONS, Drug-Drug Interactions**).

Concomitant administration of mefloquine and drugs known to lower the epileptogenic threshold may increase the risk of convulsions. (See **DRUG INTERACTIONS, Drug-Drug Interactions**).

Neuropsychiatric
Mefloquine may cause neuropsychiatric adverse reactions in adults and children. Neuropsychiatric symptoms can be difficult to identify in children; vigilance is required to monitor for the occurrence of these symptoms, especially in non-verbal children.

Psychiatric symptoms ranging from anxiety, paranoia-and depression to hallucinations and psychotic behavior, can occur with mefloquine use. Symptoms may occur early in the course of mefloquine use and on occasions, these symptoms have been reported to continue long after mefloquine has been stopped. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed. Mefloquine should not be prescribed for prophylaxis in patients with active depression or with a history of psychiatric disturbances (including depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders). During prophylactic use, if signs of acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.

Dizziness or vertigo, a disturbed sense of balance, tinnitus and other disorders of the central or peripheral nervous system have been reported during and after the use of MEFLOQUINE. Caution should be exercised with regard to driving, piloting airplanes, operating machines, deep sea diving or any other activity requiring alertness and fine motor coordination. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months or years after discontinuation of mefloquine, and in some cases vestibular damage may be permanent (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving mefloquine. During prophylactic use, if neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted.

Ophthalmologic

Any patient presenting with a visual disorder should be referred to an ophthalmologist as certain

conditions (retinal disorders or optic neuropathy) may require discontinuation of mefloquine. Periodic ophthalmologic examinations are recommended if mefloquine is to be administered for a prolonged period.

Renal

No pharmacokinetic studies have been performed in patients with renal insufficiency since only a small proportion of the drug is eliminated renally. Mefloquine and its main metabolite are not appreciably removed by hemodialysis.

Resistance

Geographical drug resistance patterns of *P. falciparum* occur, and the preferred choice of malaria prophylaxis might be different from one area to another. For example, resistance of *P. falciparum* to mefloquine has been reported, predominantly in areas of multi-drug resistance in South-East Asia. Cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed in some regions. For current advice on geographical resistance patterns, national expert centres should be consulted.

Sexual function/Reproduction

Fertility studies with mefloquine in rats have demonstrated adverse effects on fertility in males at the high dose (50 mg/kg/day) and in females at the mid and high dose (20 and 50 mg/kg/day). Administration of 250 mg/week of mefloquine (base) to adult males for 22 weeks failed to reveal any deleterious effects on human spermatozoa.

Special Populations

Nursing Mothers

Based on a study in a few subjects, low concentrations (3-4%) of mefloquine were excreted in human milk following a dose equivalent to 250 mg of the free base. The amount of mefloquine excreted in the milk is of no prophylactic value to the infant. Caution should be exercised when mefloquine is administered to a nursing woman.

Pregnant Women

Mefloquine crosses the placenta. Administered at 5 -20 times the therapeutic dose in man, mefloquine was teratogenic in mice and rats, and embryotoxic in rabbits. However, data from published studies in pregnant women have shown no increase in the risk of teratogenic effects or adverse pregnancy outcomes following mefloquine treatment or prophylaxis during pregnancy. Because the studies in humans cannot rule out the possibility of harm, mefloquine should be used during pregnancy only if clearly needed.

Women of childbearing potential should be advised to practice contraception during malaria prophylaxis with MEFLOQUINE and for 3 months after the last dose. However, in the case of unplanned pregnancy, malaria prophylaxis with mefloquine is not considered an indication for pregnancy termination. Major congenital malformations occur with a frequency of about 2 to 5 in 100 live newborns in the population at large. The reported birth prevalence of malformations in association with mefloquine falls within this range. No specific pattern of congenital malformations could be identified.

Pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

Pediatrics (< 18 years of age)

No relevant age-related changes have been observed in the pharmacokinetics of mefloquine. Therefore the dosage for children has been extrapolated from the recommended adult dose. Experience with mefloquine in infants less than 3 months old or weighing less than 5 kg is limited.

Two studies were conducted to assess the effects of mefloquine on children living in endemic areas for *P. falciparum*. All children in these studies had at least a low level of parasitemia and 18-40% had significant parasitemia with or without mild malaria symptoms. When given 20-30 mg/kg of mefloquine as a single dose, nausea and vomiting occurred in approximately 10-20%, and dizziness was seen in approximately 40% of children. Early vomiting was cited in some reports as a possible cause of treatment failure. If a second dose is not tolerated, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time.

The incidence of adverse reactions was higher than that observed in adults.

Geriatrics (≥ 65 years of age)

No relevant age-related changes have been observed in the pharmacokinetics of mefloquine.

Clinical studies of mefloquine did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Since electrocardiographic abnormalities have been observed in individuals treated with mefloquine and underlying cardiac disease is more prevalent in elderly than in younger patients, the benefits of mefloquine therapy should be weighed against the possibility of adverse cardiac effects in elderly patients. (see **WARNINGS AND PRECAUTIONS**)

Race

Pharmacokinetic differences have been observed between various ethnic populations. In practice, however, these are of minor importance in terms of drug efficacy compared with host immune status and sensitivity of the parasite.

Monitoring and Laboratory Tests

During clinical trials, this drug was not administered for longer than one year. If mefloquine is to be administered for a prolonged period, periodic evaluations including liver function tests should be performed. Although retinal abnormalities seen in humans with long-term chloroquine use have not been observed with mefloquine use, long-term feeding of mefloquine to rats resulted in dose-related ocular lesions (retinal degeneration, retinal edema and lenticular opacity at 12.5 mg/kg/day and higher). Therefore, periodic ophthalmic examinations are recommended. (see **TOXICOLOGY**)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

At the doses used for treatment of acute malaria infections, the symptoms possibly attributable to drug administration cannot be distinguished from those symptoms usually attributable to the disease itself.

Among subjects who receive MEFLOQUINE (mefloquine hydrochloride) for prophylaxis of malaria, the most frequently observed adverse experiences are nausea, vomiting, headache and dizziness.

The profile of mefloquine adverse events is characterized by a predominance of neuropsychiatric adverse events.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Among subjects who received mefloquine for prophylaxis of malaria, the most frequently observed adverse experience was vomiting (3%). Dizziness, syncope, extrasystoles and other complaints affecting less than 1% were also reported.

Among subjects who received mefloquine for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhea, skin rash, abdominal pain, fatigue, loss of appetite, and tinnitus. Those side effects occurring in less than 1% included bradycardia, emotional problems, pruritus, asthenia, and telogen effluvium (loss of resting hair). Seizures have also been reported.

Two serious adverse reactions were cardiopulmonary arrest in one patient shortly after ingesting a single prophylactic dose of mefloquine while concomitantly using propranolol (see **DRUG INTERACTIONS, Drug-Drug Interaction**), and encephalopathy of unknown etiology during

prophylactic mefloquine administration. The relationship of encephalopathy to drug administration could not be clearly established.

Post-Market Adverse Drug Reactions

The most frequently reported adverse events are:

Ear and Labyrinth Disorders: vertigo.

Gastrointestinal Disorders: nausea, vomiting, loose stools or diarrhea and abdominal pain.

Nervous System Disorders: dizziness, loss of balance, headache and somnolence.

Psychiatric Disorders: sleep disorders (insomnia, abnormal dreams).

Less frequently reported adverse events include:

Blood and Lymphatic System Disorders: agranulocytosis, aplastic anemia.

Cardiac Disorders: tachycardia, palpitation, QT prolongation, bradycardia, irregular heart rate, extrasystoles, A-V block and other transient cardiac conduction alterations.

Eye Disorders: visual disturbances.

Ear and Labyrinth Disorders: vestibular disorders including tinnitus and hearing impairment.

Gastrointestinal Disorders: dyspepsia.

General Disorders and Administration Site Disorders: edema, chest pain, asthenia, malaise, fatigue, chills, pyrexia.

Hepatobiliary Disorders: drug-related hepatic disorders from asymptomatic transient transaminase elevations to hepatic failure.

Immune System Disorders: hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis.

Investigations: Decreased hematocrit, transient elevation of transaminases, leukopenia or leukocytosis, and thrombocytopenia.

Metabolic and Nutrition Disorders: anorexia.

Musculoskeletal and Connective Tissue Disorders: muscle weakness, muscle cramps, myalgia, arthralgia.

Nervous System Disorders: syncope, convulsions, abnormal co-ordination, memory impairment, sensory and motor neuropathies (including paresthesia, tremor and ataxia) and encephalopathy.

Psychiatric Disorders: emotional problems (agitation, restlessness, anxiety, depression, mood swings, panic attacks, aggression, psychotic or paranoid reactions), confusional state, hallucinations, suicidal ideation and suicide.

Note:
In the literature, the incidence of serious neuropsychiatric adverse drug reactions (eg. seizures, psychotic reactions) with mefloquine has been reported at 1/215 following treatment and 1/11,000 following prophylactic use.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, pneumonitis of possible allergic etiology.

Skin and Subcutaneous Tissue Disorders: rash, exanthema, erythema, urticaria, pruritus, alopecia, hyperhidrosis, erythema multiforme, and Stevens-Johnson syndrome.

Vascular Disorders: circulatory disturbances (hypotension, hypertension, flushing).

Adverse reactions to MEFLOQUINE may occur or persist up to several weeks after discontinuation of the drug due to the long half-life of mefloquine. In a small number of patients it has been reported that neuropsychiatric reactions (eg. depression, tinnitus, dizziness or vertigo and loss of balance) may continue for months or years after discontinuation of MEFLOQUINE, and permanent vestibular damage has been seen in some cases.

DRUG INTERACTIONS

Overview

Mefloquine is metabolized in the liver by the cytochrome P450 system. Mefloquine does not inhibit or induce the cytochrome P450 enzyme system. It is therefore not expected that the metabolism of drugs given concomitantly with mefloquine is affected. However, inhibitors or inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentrations, respectively.

Inhibitors of CYP3A4
In a pharmacokinetic study in healthy volunteers (N=8) receiving single dose of 500 mg mefloquine alone or co-administration with 400 mg/day ketoconazole orally for 10 days showed that the co-administration of ketoconazole, a strong inhibitor of CYP3A4, increased the mean

plasma concentrations of mefloquine (AUC_{0-t} by 79% and Cmax by 64%) and elimination half-life ($t_{1/2}$ by 39%).

Inducers of CYP3A4
In another pharmacokinetic study in healthy volunteers (N=7) receiving a single dose of 500 mg mefloquine plus a long-term administration of 600 mg of rifampicin a potent inducer of CYP3A4 reduced the plasma concentrations of mefloquine ($AUC_{0-\infty}$ by 68% and Cmax by 19%) and elimination half-life ($t_{1/2}$ by 63%).

Substrates and inhibitors of P-glycoprotein
It has been shown in vitro that mefloquine is a substrate and an inhibitor of P-glycoprotein. Therefore, drug-drug interactions could also occur with drugs that are substrates or are known to modify the expression of this transporter. The clinical relevance of these interactions is not known to date.

Drug-Drug Interactions

Drug-drug interactions with mefloquine have not been explored in detail.

Concomitant administration of mefloquine and quinine, quinidine, or chloroquine may produce electrocardiographic abnormalities. If quinine or quinidine are to be used in the initial treatment of severe malaria, mefloquine administration should be delayed for at least 12 hours after the final dose of either of these drugs. Caution should also be exercised with other drugs that alter cardiac conduction (e.g., anti-arrhythmics, β-adrenergic blocking agents, calcium channel blockers, antihistamines or H_1-blocking agents (astemizole, terfenadine), tricyclic antidepressants and phenothiazines) since they may contribute to a prolongation of the QTc interval.

There is evidence that the use of halofantrine during mefloquine therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of mefloquine, causes a significant lengthening of the QTc interval (see **WARNINGS AND PRECAUTIONS).** Due to increased plasma concentrations and elimination half-life of mefloquine following co-administration with ketoconazole, the risk of QTc prolongation may also be expected if ketoconazole is taken during mefloquine therapy for prophylaxis or treatment of malaria or within 15 weeks after the last dose of mefloquine (see **WARNINGS AND PRECAUTIONS**). Clinically significant QTc interval prolongation has not been found with mefloquine alone.

A patient with previous myocardial infarction suffered a cardiopulmonary arrest five hours after taking mefloquine. Propranolol and chloroquine were also taken. That patient recovered fully.

Concomitant administration of mefloquine with drugs known to lower the epileptogenic threshold (antidepressants; bupropion; antipsychotics; tramadol; quinine, quinidine or chloroquine) may increase the risk of convulsions.

Patients taking mefloquine while taking valproic acid had loss of seizure control and lower than expected valproic acid blood levels. Therefore, patients concurrently taking antiseizure medication, including valproic acid, carbamazepine, phenobarbital, and phenytoin, and mefloquine should have the blood level of their antiseizure medication monitored and the dosage adjusted appropriately.

In clinical trials, the concomitant administration of sulfadoxine and pyrimethamine did not alter the adverse reaction profile.

When mefloquine is taken concurrently with oral live typhoid vaccines, attenuation of immunization cannot be excluded. Vaccinations with attenuated live bacteria should therefore be completed at least three days before the first dose of mefloquine.

A controlled clinical study was carried out in 20 subjects to investigate a potential interaction between mefloquine and alcohol. The blood alcohol concentrations attained in the patients taking mefloquine (0.3-0.5 mg/mL), did not impair coordinated psychomotor activities. A single case in the literature reports a transient severe psychiatric disturbance, suggesting an adverse reaction to mefloquine associated with a heavy ingestion of alcohol (600 mL of whisky).

Mefloquine is highly bound (98%) to plasma proteins.

No other drug interactions have been reported. Nevertheless, the effects of mefloquine on travelers receiving co-medication, particularly diabetics or patients using anticoagulants, should be checked before departure.

DOSAGE AND ADMINISTRATION

Dosing Considerations

MEFLOQUINE (mefloquine hydrochloride) should be taken with food, and with at least 8 oz (240 mL) of liquid. All dosage instructions relate to the mefloquine base. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

Recommended Dose and Dosage Adjustment

Prophylaxis

The recommended prophylactic dose of MEFLOQUINE is approximately 5 mg/kg once weekly (to a maximum of 250 mg).

1. Adults and children weighing over 45 kg
   In persons over 45 kg, the prophylactic dose is 250mg of mefloquine (one MEFLOQUINE tablet) once weekly.
2. Children and adults weighing less than 45 kg
   The weekly dose decreases in proportion to bodyweight.

Weight (kg)	Dose
> 30-45 kg	¾ tablet
>20-30 kg	½ tablet
5 to 20 kg	¼ tablet

Experience with mefloquine in infants less than 3 months old or weighing less than 5 kg is limited. Children weighing between 5 to 10 kg will receive a higher prophylactic dose of mefloquine than the recommended 5 mg/kg; however the tablet cannot be accurately subdivided into less than ¼ tablet.

The first dose should be taken at least one week before arrival in an endemic area. Weekly doses should always be taken on the same day of the week. To reduce the risk of malaria after leaving an endemic area, prophylaxis must be continued for 4 additional weeks.

Consideration may also be given to initiating mefloquine prophylaxis 2 to 3 weeks prior to departure in order to determine tolerance to MEFLOQUINE and allow time to substitute other antimalarials if required.

Unexpected Travel - Loading Dose
If it is not possible to initiate therapy one week before arrival in an endemic area, data from the literature indicate that a loading dose of mefloquine can be given in order to rapidly achieve effective blood levels of the drug; in adults weighing over 45 kg this is one MEFLOQUINE tablet (250 mg mefloquine) daily for 3 days, followed thereafter by standard weekly dosing during exposure and for 4 weeks after leaving an endemic area.

Day 1	1st Dose
Day 2	2nd Dose
Day 3	3rd Dose
Thereafter	Regular weekly doses

The use of a loading dose may also permit an assessment of drug tolerance before travel and allows a change to a suitable alternative if required. The use of a loading dose may be associated with an increased incidence of adverse events (see **ADVERSE REACTIONS**).

When prophylaxis with MEFLOQUINE fails, physicians should carefully evaluate which antimalarial to use for malaria treatment. Regarding the use of halofantrine, see **WARNINGS AND PRECAUTIONS**.

Treatment
The recommended total therapeutic dose of mefloquine for non-immune patients is 20-25 mg/kg. A lower total dose of 15 mg/kg may suffice for partially immune individuals. Thus, non-immunes weighing over 45 kg should receive a total of 1250-1500 mg mefloquine (5-6 MEFLOQUINE tablets) while partially immune patients of the same weight should receive 750-1000 mg (3-4 MEFLOQUINE tablets). (See following table.)

Recommended total therapeutic dosages of MEFLOQUINE tablets relative to body-weight and immune status *

	Non-immune patients	Partially immune patients
< 20 kg **	¼ Tablet per 2.5 -3 kg of weight 1 tablet per 10 -12 kg of weight	¼ tablet per 4 kg of weight 1 tablet per 16 kg of weight
20-30 kg	2-3 tablets	1½-2 tablets
30-45 kg	3-4 tablets	2-3 tablets
45-60 kg	5 tablets	3 tablets
> 60 kg ***	6 tablets	4 tablets

* Splitting the total curative dosages into 2-3 doses (e.g. 3 + 1, 3 + 2, 3 + 2 + 1 tablets) taken 6-8 hours apart may reduce the occurrence or severity of adverse effects (see **ADVERSE REACTIONS**).

** Experience with mefloquine in infants less than 3 months old or weighing less than 5 kg is limited.

*** There is no specific experience with total dosages of more than 6 tablets in very heavy patients.

A second full dose should be given to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30-60 minutes after a dose, an additional half-dose should be given.

Patients with acute *P. vivax* malaria treated with MEFLOQUINE are at high risk of relapse because MEFLOQUINE does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse after initial treatment of the acute infection with MEFLOQUINE, patients should subsequently be treated with an 8-aminoquinoline (e.g. primaquine) in order to eliminate liver forms.

If a full treatment course with MEFLOQUINE does not lead to improvement within 48-72 hours, alternative treatments should be considered. When break through malaria occurs during MEFLOQUINE prophylaxis, physicians should carefully evaluate which antimalarial to use for therapy. Regarding the use of halofantrine, see **WARNINGS AND PRECAUTIONS**.

MEFLOQUINE can be given for severe acute malaria after an initial course of intravenous quinine lasting at least 2-3 days. Interactions leading to adverse events can largely be prevented by allowing an interval of at least 12 hours after the last dose of quinine.

OVERDOSAGE

Symptoms and signs

In cases of overdosage with MEFLOQUINE (mefloquine hydrochloride), the symptoms mentioned under **ADVERSE REACTIONS** may be more pronounced.

Treatment

Patients should be managed by symptomatic and supportive care following MEFLOQUINE overdose, particularly for cardiovascular disturbances. There are no specific antidotes. The use of activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mefloquine, a fluorinated quinoline derivative, acts on the asexual intraerythrocytic forms of the human malaria parasites: *Plasmodium falciparum, P. vivax, P. malariae* and *P. ovale*.

Pharmacokinetics

Absorption: The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formulation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. Plasma concentrations peak 6-24 hours (median, about 17 hours) after a single oral dose of mefloquine. Maximum plasma concentrations in μg/L are roughly equivalent to the dose in milligrams (for example, a single 1000 mg dose produces a maximum concentration of about 1000 μg/L). At a dose of 250 mg once weekly, maximum steady state plasma concentrations of 1000-2000 μg/L are reached after 7-10 weeks.

Distribution: In healthy adults, the apparent volume of distribution is approximately 20 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes at an erythrocyte-to-plasma concentration ratio of about 2. Protein binding is about 98%. Mefloquine blood concentrations of 620 ng/mL are considered necessary to achieve 95% prophylactic efficacy.

Mefloquine crosses the placenta (see **WARNINGS AND PRECAUTIONS**, **Pregnant Women**). Excretion into breast milk appears to be minimal (see **WARNINGS AND PRECAUTIONS, Pregnant Women**).

Metabolism: Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. *In vitro* and *in vivo* studies strongly suggested that CYP3A4 is the major isoform involved. Two metabolites of mefloquine have been identified in humans. The main metabolite, 2-8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive against *P. falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose of mefloquine. Maximum plasma concentrations of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug.

The other metabolite, an alcohol, was present in only minute amounts only.

Excretion: In several studies in healthy adults, the mean elimination half-life of mefloquine varied between 2 and 4 weeks, with an average of about 3 weeks. Total clearance, which is essentially hepatic, is in the order of 30 mL/min. There is evidence that mefloquine is excreted mainly in the bile and feces. In volunteers, urinary excretion of unchanged mefloquine and its main metabolite accounted for about 9% and 4% of the dose, respectively. Concentrations of their metabolites could not be measured in the urine.

During long-term prophylaxis the elimination half-life of mefloquine remains unchanged.

STORAGE AND STABILITY

Store 15-30^{o}C. Sensitive to moisture. Keep in the blister until consumed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

In addition to the active ingredient (mefloquine hydrochloride) each MEFLOQUINE 250 mg tablet contains the non-medicinal ingredients microcrystalline cellulose, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide.

MEFLOQUINE 250 mg: Each white, round, biconvex tablet, cross scored on one side, and plain on the other side, contains 250 mg mefloquine (base) as mefloquine hydrochloride. Available in blister packs of 8's.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

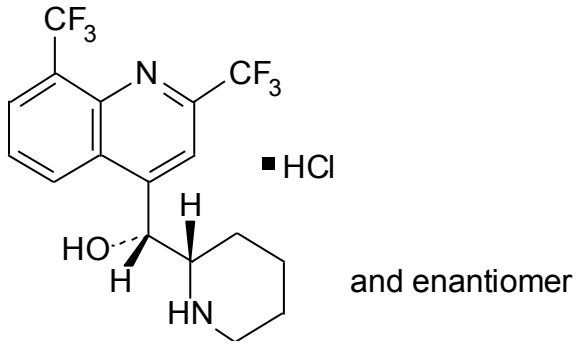
Drug Substance

Common name: Mefloquine Hydrochloride

Chemical name: DL-Erythro-α-(2-piperidyl)-2, 8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride

Molecular formula and molecular mass: $C_{17}H_{16}F_6N_2O \bullet HCl$ and 414.79

Structural formula:



Physicochemical properties: Mefloquine is a 4-quinoline methanol derivative. It is a 2-aryl substituted chemical structural analog of quinine. The drug is a white to almost white crystalline powder. The solubility in water is 0.35 g/100 mL at 25°C. The pH of a 1% aqueous suspension is 5.0-6.5. The pka value is approximately 9. The substance melts at approximately 252°C with decomposition.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study was performed using healthy volunteers. The rate and extent of absorption of mefloquine HCl was measured and compared following oral administration of a single 1 x 250 mg dose of MEFLOQUINE (mefloquine HCl) tablets, or Lariam® (mefloquine HCl) tablets, under fed conditions. The results from measured data are summarized below.

Summary Table of the Comparative Bioavailability Data
Mefloquine (Dose: 1 x 250 mg) From Measured Data – Under Fed Conditions

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	MEFLOQUINE	Lariam®†	
AUC_T (μg•h/mL)	17.4 18.0 (27)	18.0 18.7 (27)	96.4 (87.0 – 106.8)
AUC_I (μg•h/mL)	73.8 86.8 (65)	65.7 75.4 (53)	102.1# (89.6 – 116.3)
C_{max} (μg/mL)	0.344 0.355 (24)	0.352 0.358 (19)	97.9 (89.7 – 106.8)
T_{max} (h)*	8.29 (42)	9.19 (102)	-
$t_{1/2}$ (h)*	203 (73)	180 (51)	-

* Arithmetic means (CV%).
** Based on the least squares estimate.
# Based on Kel (λ) as the covariate
† Lariam® is manufactured by Hoffmann La Roche Limited, and was purchased in Canada.

PARASITOLOGY

Mechanism of Action

Mefloquine is an antimalarial agent which acts as a blood schizonticide. Its exact mechanism of action is not known.

Activity *In Vitro* and *In Vivo*

In Vitro Studies
Below are results of mefloquine's ability, at varying concentrations, to inhibit the maturation of *P. falciparum* trophozoites formed in red blood cells.

Strain	ED_{50} (µg/L)
Drug-sensitive isolate from Africa	41.5
Drug-resistant isolate from South Vietnam	46.2

More sophisticated *in vitro* studies were performed later by using parasites from continuous culture of *P. falciparum*. These studies also showed no significant cross resistance against isolates obtained from a patient with malaria caused by *P. falciparum* resistant to multiple drugs.

Strain	ED_{50} (µg/L)
Drug-sensitive isolate from Africa	6.7 ± 1.0
Drug-resistant isolate from South Vietnam	7.8 ± 1.4

A study was performed to establish an *in vitro* culture system of four strains of *P. falciparum* to determine the antimalarial activity of mefloquine and reference antimalarials employing incorporation of ^{3}H-hypoxanthine into RNA and DNA of the parasite as an endpoint.

The rate of hypoxanthine uptake is taken as a measure of parasite growth. The ID_{50}, i.e., the concentration causing 50% inhibition of uptake of [G-^{3}H]-hypoxanthine in the four strains of *P. falciparum* by mefloquine is shown below.

P. falciparum Isolate	ID_{50} (µg/L)
Geneva 13	120.1
East Africa	138.0
FD-III V	127.0
Z	131.6

The in *vitro* culture of *P. falciparum* strains and inhibition of hypoxanthine incorporation into DNA and RNA of the parasite is a rapid reproducible assay for antimalarial activity that can supplement the *in vitro* mouse assay.

In Vivo Studies
Rodent Studies
Studies of the antimalarial activity of mefloquine in mice were done with a variety of strains of rodent malaria with varying drug sensitivity patterns.

Mefloquine showed marked prophylactic activity when given in single oral doses of 5 to 200 mg/kg 6 to 96 hours before infection.

A study was performed to determine the ability of mefloquine to prevent malaria by exoerythrocytic effect (causal prophylaxis), and it was shown that mefloquine, given at 300-1,000 mg/kg S.C. to mice infected with *P.y. nigeriensis* was minimally active at 300 and fully active at 1,000 mg/kg. Mefloquine was not active when given to chicks infected with *P. gallinaceum* at 15-480 mg/kg in peanut oil. The apparent prophylactic activity against *P.y. nigeriensis* was probably related to persistence of the drug with resulting activity on erythrocytic forms. Studies in which mefloquine was administered prior to inoculation of mice with *P.y. yoelii* showed such a persistent effect.

After infection was established, the onset of antimalarial activity was found to be slow and occurred 48 hours after drug treatment.

A study was performed to determine the chemotherapeutic activity of mefloquine against *P. berghei* in mice using varying dosage regimens. Mice that were tested for suppressive activity were given I.P. erythrocytes that were infected with strain Anka of *P. berghei* and received four oral doses six hours before and 24, 48 and 72 hours after infection. The ED_{50} and ED_{90} of mefloquine were 1.8 and 4.0 mg/kg, respectively.

Experimental studies were performed in mice infected with *P. berghei* to assess the activity of mefloquine in combination with other potential new drugs. Results were additive when mefloquine was combined with the following drugs: 5-Fluroorotic acid, two types of quinolinemethanols, a phenanthrenemethanol, pyrimethamine and sulfaphenazole.

Simian Studies
Antimalarial studies with mefloquine were initially performed in rhesus monkeys infected with *P. cynomolgi*. The infections were cured by daily oral doses of 10 or 31.6 mg/kg/day for two days.

Mefloquine was tested in 100 New World owl monkeys (Aotus trivirgatus) infected with *Plasmodium falciparum* and showed remarkable activity. Mefloquine was nearly equally effective against both drug sensitive and drug resistant strains of *P. falciparum*. There appeared to be little difference in cure rates whether the drug was given orally in single doses or whether the same dose was divided into daily increments. The results are shown below.

Isolate	Total Dose (mg/kg)	Number of Daily Doses	Results Cured/Total
Chloroquine-susceptible	≤ 2.74	1-7	0/18
	5.48	1	2/3
	5.48	3	1/3
	10.94	1	6/7
	10.94	3	6/6
	10.94	7	4/8
	21.9	7	5/6
	≥43.75	1-7	19/19
Chloroquine-Resistant OK strain	≤5.48	1-7	0/25
	10.94	1	3/3
	10.94	3	3/6
	10.94	7	5/7
	21.9	3	2/3
	21.9	7	2/5
	≥43.75	1-7	18/19

The activity of mefloquine administered intravenously was also studied in the New World owl monkey. Doses of 30 mg/kg, administered as a single dose or divided into equal daily doses of 10 mg/kg/day for three days, was uniformly curative.

The activity of mefloquine against relapsing malaria was assessed in sporazoite induced infections in monkeys. The initial studies used *P. cynomolgi* in rhesus monkeys. When the drug was administered for nine days beginning two days before sporozoite inoculation, no causal prophylactic activity was detected at doses up to 20 mg/kg/day.

Additional studies in the same model were performed to evaluate the effect of mefloquine on persistent exoerythrocytic forms (hypnozoite). Chloroquine was administered in doses known to eliminate erythrocytic forms of the parasite. Concurrently, mefloquine was administered in daily oral doses up to 40 mg/kg/day for seven days. All infections reoccurred indicating that mefloquine has no significant exoerythrocytic activity. However, doses of 10 mg of mefloquine per kg per day for seven days were uniformly curative in this model when given in combination with primaquine, a drug with known exoerythrocytic activity.

The activity against erythrocytic forms of *P. vivax* was studied in owl monkeys infected with this parasite. The drug was found to be more effective against this parasite than against *P. falciparum*.

Cross-Resistance Studies

Mefloquine is active against malarial parasites resistant to other antimalarials such as chloroquine and other 4-aminoquinoline derivatives, proguanil pyrimethamine and pyrimethamine-sulfonamide combinations.

Resistance to a variety of standard antimalarial drugs was induced in strains of rodent malaria in order to determine cross-resistance with new antimalarial drugs. Results of various studies for cross-resistance with mefloquine are shown in Table 2.

TABLE 2

Strain	Cross-Resistance Factor*
chloroquine-resistant *P. berghei*	20, > 91, 1.8, 2.4
chloroquine-resistant *P. vinckei*	2
triazine-resistant *P. berghei*	1.3, 0.8
sulphone-resistant *P. berghei*	1.1
quinine-resistant *P. berghei*	> 83
pyrimethamine-resistant *P. berghei*	0.7

* Cross-resistance factor obtained by dividing the dose mefloquine required for 90% suppression of parasitemia (SD_{90}) in the resistant strain by the SD_{90} of mefloquine in the parent or drug-sensitive strain.

Resistance to mefloquine was induced in mice infected with *P. berghei*. After nine weekly passages, a greater than 20-fold degree of resistance had developed. The rate of induction was faster than with chloroquine. By combining mefloquine with pyrimethamine, primaquine or sulfaphenazole, the rate of the development of resistance to mefloquine was decreased.

Cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed in some regions.

TOXICOLOGY

Teratology/Embryotoxicity Studies

Mefloquine administered to pregnant mice, rats, and rabbits was teratogenic at doses similar to the clinical acute treatment dose of 21 to 25 mg/kg, based on body surface area comparisons. In all three animal species, CNS effects (e.g., exencephaly, hydrocephaly or partially missing medulla oblongata) and craniofacial malformations were observed. At the same doses, mefloquine was also embryotoxic in mice and rabbits. All of these findings were observed at doses that were maternally toxic.

Mutagenicity Studies

Mefloquine was not found to be mutagenic in the following tests: Ames Test, Fluctuation Test, Host (Mouse) Mediated Assay, Micronucleus Test, Induction of Point Mutations, Yeast Treat and Plate Test.

Carcinogenicity

Two year studies were performed with both BDF_1 mice and Long Evans Hooded rats with the maximum dose group receiving 30 mg/kg/day. Carcinogenic effects related to mefloquine administration were not observed.

Special Toxicity Studies

Ocular lesions were observed in rats fed mefloquine daily for 2 years. All surviving rats given 30 mg/kg/day had ocular lesions in both eyes characterized by retinal degeneration, opacity of the lens, and retinal edema. Similar but less severe lesions were observed in 80% of female and 22% of male rats fed 12.5 mg/kg/day for 2 years. At doses of 5 mg/kg/day, only corneal lesions were observed. They occurred in 9% of rats studied.

Male Wistar rats orally administered-mefloquine daily for 22 days at the equivalent human therapeutic plasma concentration showed CNS penetration of mefloquine, with a 30-50 fold greater brain/plasma drug ratio up to 10 days after the final dose administered.

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45. Product Monograph - PrLARIAM® (mefloquine hydrochloride tablets) 250 mg. Hoffmann-La Roche Limited Control No. 126525. Date of Revision: March 03, 2011.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

MEFLOQUINE
Mefloquine Tablets
250 mg mefloquine (as mefloquine hydrochloride)

Read this carefully before you start taking **MEFLOQUINE** 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 **MEFLOQUINE**.

The Patient Medication Information leaflet for MEFLOQUINE is intended only for travellers who are taking MEFLOQUINE to prevent malaria. The information may not apply to patients who are sick with malaria and who are taking MEFLOQUINE to treat malaria.

Serious Warnings and Precautions

- MEFLOQUINE may not be right for you. Tell your healthcare professional if you suffer from any mental health illness that affect mood, thinking and behavior such as depression, anxiety, psychosis, schizophrenia – either now, or in the past.

- **MEFLOQUINE can cause serious mental problems in some people.** These serious side effects may occur suddenly and may last for months to years after stopping MEFLOQUINE. Symptoms of serious mental problems may include:
  - anxiety
  - unreasonable feeling that people are trying to harm you, do not like you, etc. (Paranoia)
  - depression
  - seeing or hearing things that are not there (hallucinations)
  - thought of suicide or harming yourself
  - feeling restless,
  - feeling confused
  - unusual behavior

- **MEFLOQUINE can cause serious nervous system problems in some people**. Symptoms of serious nervous system problems may include:
  - dizziness
  - a feeling that you or things around you are moving or spinning (vertigo)
  - loss of balance
  - ringing sound in your ears (tinnitus)
  - convuslions (seizures) in people who already have seizures (epilepsy)
  - unable to sleep (insomnia)
  - dizziness, vertigo, tinnitus, and loss of balance

- These serious mental and nervous system side effects may occur at any time while you are taking MEFLOQUINE, may last for months or years after stopping MEFLOQUINE, and in some cases may become permanent in some people.

- Seek medical help right away if you have any of the symptoms listed above. You may have to stop Mefloquine because of its side effects. If you stop Mefloquine, you will need another medicine to prevent malaria.

- An information wallet card is provided at the end of this leaflet. Cut it out and carry it with you when you are taking MEFLOQUINE.

What is MEFLOQUINE used for?

MEFLOQUINE is a medicine used to treat and prevent Malaria.
Malaria is a serious disease that is spread by mosquitoes in certain parts of the world.

How does MEFLOQUINE work?
MEFLOQUINE is a medicine that belongs to a class of drugs called antimalarials. It works by killing the small living things (parasites) that cause malaria.

What are the ingredients in MEFLOQUINE?
Medicinal ingredients: mefloquine hydrochloride
Non-medicinal ingredients: microcrystalline cellulose, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide

MEFLOQUINE comes in the following dosage forms:
MEFLOQUINE 250 mg: Each white, round, biconvex tablet, cross scored on one side, and plain on the other side, contains 250 mg mefloquine (as mefloquine hydrochloride). Available in blister packs of 8's.

Do not use MEFLOQUINE if you have currently, or in the past, suffer from:

- An allergy to MEFLOQUINE, similar medicines such as quinine or quinidine or any ingredients in MEFLOQUINE (see "What are the ingredients in MEFLOQUINE?" section above).
- Any mental health illness that affects mood, thinking and behavior such as :
  - depression
  - anxiety
  - psychosis
  - schizophrenia
- Seizures (fits).

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

- Have currently, or in the past suffer from any mental health problems that affect mood, thinking and behavior such as :
  - depression,
  - anxiety
  - psychosis,
  - Schizophrenia

  See the serious Warnings and Precautions box above.
- Have heart disease, especially a rare heart problem that may cause irregular heartbeat, fainting, or sudden death (QT prolongation).
- Have liver problems

- Have seizures or epilepsy
- Have diabetes
- Have anemia (a lower than normal number of red bloods cells)
- Have eye problems
- Have blood clotting problems or take blood thinner medicines (anticoagulants)
- Are pregnant. Tell your healthcare professional if you are pregnant or plan to become pregnant. It is not known if MEFLOQUINE is safe in pregnancy. Use birth control while you are taking MEFLOQUINE and for 3 months after you stop MEFLOQUINE. Tell your healthcare professional right away; if you get pregnant while taking MEFLOQUINE.
- Are breast feeding or plan to breast feed. MEFLOQUINE can pass through your milk and may harm the baby. Therefore, ask a healthcare professional whether you will need to stop breast feeding or use another medicine.

Other warnings you should know about:

Protect yourself against Mosquito bites. MEFLOQUINE decreases your risk of getting malaria. However MEFLOQUINE does not guarantee that you will not become sick. There is a chance you could still get malaria during or after taking MEFLOQUINE. Take the following steps to avoid mosquito bites while in an area where malaria is common:

- Wear long sleeves and long pants
- Use mosquito repellants
- Sleep in a room that is screened against mosquitoes or use a bed net

If you develop a fever or flu-like symptoms during your travels or within 2 to 3 months after you leave the malaria area, contact your healthcare professional right away.

If you cannot continue taking MEFLOQUINE due to side effects or for other reasons, contact a healthcare professional immediately.

If you take MEFLOQUINE for a year or longer, your healthcare professional should check:

- your eyes, especially if you have trouble seeing while you take MEFLOQUINE
- your liver function to see if there has been damage to your liver.

Do not drive or perform activities requiring alertness and careful movements (fine motor coordination) until you know how MEFLOQUINE affects you. You may feel dizzy or lose your balance. This could happen for months after you stop taking MEFLOQUINE.

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 MEFLOQUINE:

- Medicines that may cause serious heart problems which can cause death
    - Halofantrine used to treat malaria (no longer available in Canada)
    - Ketoconazole used to treat fungal infections

Do not take halofantrine or ketoconazole if you are already taking, or have taken MEFLOQUINE within the last 15 weeks.

- Other medicines to prevent or treat malaria such as quinine, quinidine or chloroquine. **Do not** take quinine or chloroquine with MEFLOQUINE. You may have a greater risk for seizures or serious heart problems.
- Medicines to treat heart problems or high blood pressure:
  - anti-arrhythmic medicines,
  - beta-adrenergic blocking medicines such as atenolol, metoprolol, propranolol
  - calcium channel blockers such as amlodipine, diltiazem, nifedipine,verapamil
- Medicines used to treat allergies (antihistamines or H1-blocking agents)
- Medicines used to treat depression:
  - Tricyclic anti-depressants such as amitriptyline, nortriptyline
  - selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram
  - bupropion
- Medicines used to treat mental problems such as phenothiazines
- Tramadol (a pain killer)
- Medicines used to treat seizures such as valproic acid, carbamazepine, phenobarbital, and phenytoin.
- Medicines to treat infections such as rifampicin
- Medicines for diabetes
- Blood thinner medicines (anticoagulants)

Some of these drugs may increase your chance of having serious side effects. Your healthcare professional may need to change the dose of your medications or check you regularly for side effects.

In addition:
Be aware that certain vaccines may not work if given while you are taking MEFLOQUINE. Your healthcare professional may want you to finish taking your vaccines at least 3 days before starting MEFLOQUINE.

MEFLOQUINE may interact with alcohol and increase your risk of experiencing mental problems. Limit alcohol intake while taking mefloquine and do not drink alcohol on the day you take your mefloquine tablet for malaria prevention.

How to take MEFLOQUINE:

To Prevent Malaria

- **Adults and pediatric patients weighing over 45 kg**: Take 1 tablet of MEFLOQUINE **once a week,** on the same day each week.
- **Adult or pediatric patient weighing 45 kg (99 pounds) or less:** Your doctor will decide the right dose for you.
- MEFLOQUINE is not recommended in children less than 3 months old or weighing less than 5 kg.

Important:

- Take the tablet once a week (on the same day each week).
- Take the first dose of MEFLOQUINE at least 2 weeks before you travel to a malaria area. This is to help you see how MEFLOQUINE affects you and the other medicines you take.
- Continue to take MEFLOQUINE on the same day of the week throughout your stay and for **4 weeks after you return.**
- Take MEFLOQUINE just after a meal and with at least 1 cup (8 ounces) of water; **do not** take MEFLOQUINE on an empty stomach.
- If you vomit after taking MEFLOQUINE, contact your doctor to see if you should take another dose.
- For children or people who cannot swallow MEFLOQUINE Tablets whole: the tablets may be crushed and mixed with small amount of water, milk or other beverage.
- Your healthcare professional will tell you the correct dose for your child based on his weight.
- Take MEFLOQUINE exactly as your healthcare professional tells you to take it.

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To Treat Malaria:

Your healthcare professional will tell you how much medicine you need to take.

Overdose:

If you think you have taken too much **MEFLOQUINE**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget a dose of MEFLOQUINE, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose and follow your usual schedule. **Do not** take a double dose (two doses on the same day) to make up for a forgotten dose.

What are possible side effects from using MEFLOQUINE?

These are not all the possible side effects you may feel when taking MEFLOQUINE. If you experience any side effects not listed here, contact your healthcare professional. Please also see the SERIOUS **WARNINGS AND PRECAUTIONS BOX** at the beginning of the leaflet.

MEFLOQUINE, like all medicines, may cause side effects in some patients. The most frequently reported side effects with MEFLOQUINE when used for prevention of malaria include:

- nausea
- vomiting
- diarrhea
- abdominal pain
- dizziness or loss of balance (vertigo), which in some people may continue for months after stopping MEFLOQUINE
- headache

- sleep problems (difficulty sleeping, bad dreams)

Tell your doctor if any of the side effects listed above bother you or do not go away.

The most common side effects in people who take Mefloquine for treatment include:

- dizziness
- muscle pain
- nausea
- fever
- headache
- vomiting
- chills
- diarrhea,
- skin rash
- abdominal pain
- fatigue
- loss of appetite
- ringing in the ears

MEFLOQUINE may cause serious mental and serious nervous system problems in some patients (see the **Serious Warnings and Precautions box at the beginning of this leaflet and the serious side effects table below**).

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	
Frequency : Not known (cannot be estimated from the available data): **Effect: Serious Mental Problems:** **Symptoms:** • severe anxiety • depression • unreasonable feeling that people are trying to harm you, do not like you, etc. (Paranoia) • seeing or hearing things that are not there (hallucinations) • thoughts of suicide or harming yourself • feeling restless, • feeling confused • feeling disoriented • unusual behavior • unusual changes in your mood • panic attacks			√
Frequency : Not known			√

Effect : Nervous system changes **Symptoms** • dizziness, a feeling that you or things around you are moving • spinning, • ringing in the ears • loss of balance • fits (seizures or convulsions)			
Frequency : Not known **Effect: Heart Problems** **Symptoms:** • abnormal heart beat or pounding, racing or skipped beats (palpitations)			√
Frequency : Not known **Effect:** inflammation of the lungs (pneumonitis) **Symptoms:** • fever • chills • cough • shortness of breath • chest pain			√
Frequency : Not known **Effect: serious liver problems:** **Symptoms: jaundice** • yellowing of skin or the white of your eyes • dark colored urine • light coloured stools • generalized itchiness			√
Frequency : Not known **Problem with the nerves** (neuropaty) **Symptoms:** • prickling or tingling sensation in the affected body part • numbness and loss of an ability to feel pain or changes in temperature, particularly in your feet • a burning or sharp pain, usually in the feet • loss of balance or co-ordination • feeling pain from a very light touch • Muscle weakness or paralysis			√
Frequency : Not known **Effect: serious disorder of the skin (Stevens Johnson syndrome)** **Symptoms:** • skin pain • red or purple skin rash • blisters on your skin and the mucous membranes of your mouth, nose, eyes and genitals • shedding of your skin			√
Frequency : Not known			√

Effect: Allergic reactions: **Symptoms:** • difficulty breathing • swelling of the face , tongue or throat • itching and severe skin rash			

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

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

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

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

Storage:
Store 15-30°C. Sensitive to moisture. Keep in the blister until consumed.

If you want more information about MEFLOQUINE:
- 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; or by contacting the sponsor, AA Pharma Inc. at 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

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Information Wallet Card to carry when you are taking MEFLOQUINE.
Please read the Patient Medication Information for additional information on MEFLOQUINE

MEFLOQUINE (mefloquine hydrochloride) Tablets – For Prevention of Malaria

You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area. MEFLOQUINE can cause serious side effects, including:

1. Serious heart problems. Do not take halofantrine or ketoconazole with MEFLOQUINE or within 15 weeks of your last dose of MEFLOQUINE. You may get serious heart problems that can lead to death. **Do not** take quinine or quinidine with MEFLOQUINE. Stop taking MEFLOQUINE if it makes your heart beat irregularly.

2. Serious mental problems. Symptoms of serious mental problems may include: severe anxiety; depression; unreasonable feeling that people are trying to harm you, do not like you, etc. (Paranoia); seeing or hearing things that are not there (hallucinations); thoughts of suicide or harming yourself; feeling restless / confused / disoriented; unusual behavior; unusual changes in your mood and panic attacks.

3. Serious nervous systems problems. Do not take quinine or chloroquine with MEFLOQUINE. You may have a greater risk for seizures. Symptoms of serious nervous system problems may include: dizziness; a feeling that you or things around you are moving or spinning; loss of balance ringing in your ears; convulsions in people who already have seizures; and unable to sleep.

Seek medical help right away if you have any of the symptoms listed above. You may have to stop Mefloquine because of its side effects. If you stop Mefloquine, you will need another medicine to prevent malaria. **These serious mental and nervous system side effects may occur at any time while your are taking MEFLOQUINE, may last for months or years after stopping MEFLOQUINE, and in some cases may be permanent.**

Revised: August 04, 2016