# PRODUCT MONOGRAPH

## PrLARIAM®

(mefloquine hydrochloride tablets)

mefloquine 250 mg

**Antimalarial Agent**

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## NAME OF DRUG

**PrLARIAM®**
(mefloquine hydrochloride tablets)
mefloquine 250 mg

## THERAPEUTIC CLASSIFICATION

Antimalarial Agent

## ACTIONS AND CLINICAL PHARMACOLOGY

LARIAM (mefloquine) acts on the asexual intraerythrocytic forms of the human malaria parasites: Plasmodium falciparum, P. vivax, P. malariae and P. ovale.

LARIAM is effective against malaria parasites resistant to other antimalarials such as chloroquine, proguanil, pyrimethamine and pyrimethamine-sulfonamide combinations.

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 (see **WARNINGS**).

### Clinical 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 dose of LARIAM. 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**, *Pregnancy*). Excretion into breast milk appears to be minimal (see **PRECAUTIONS**, *Nursing Mothers*).

*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 minute quantities only.

*Elimination*

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.

## INDICATIONS AND CLINICAL USES

*Prophylaxis:*

LARIAM (mefloquine) 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:*

LARIAM 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.

Note:

1. 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 intravenous treatment, LARIAM may be given orally to complete the course of therapy.
2. Patients with acute P. vivax malaria, treated with LARIAM, are at high risk of relapse because LARIAM does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse, after initial treatment of the acute infection with LARIAM, patients should subsequently be treated with an 8-aminoquinoline (e.g., primaquine).
3. There are insufficient clinical data to document the effect of mefloquine in malaria caused by P. ovale or P. malariae.

## CONTRAINDICATIONS

LARIAM (mefloquine) 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 LARIAM prophylactically since LARIAM may precipitate these conditions.

## WARNINGS

Concomitant administration of LARIAM (mefloquine) and quinine, quinidine, chloroquine, or drugs producing beta-adrenergic blockade may produce electrocardiographic abnormalities or cardiac arrest. Due to the risk of a potentially fatal prolongation of the QTc interval, halofantrine must not be given during LARIAM therapy for prophylaxis or treatment of malaria or within 15 weeks after the last dose of LARIAM (see **PRECAUTIONS**, **General** and **Drug Interactions**). Ketoconazole must not be administered with LARIAM therapy for prophylaxis or treatment of malaria or within 15 weeks of the last dose of LARIAM due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following coadministration (see **ACTION AND CLINICAL PHARMACOLOGY**, *Elimination* and **PRECAUTIONS**, **Drug Interactions**).

Concomitant administration of LARIAM and quinine, quinidine, or chloroquine may increase the risk of convulsions (see **PRECAUTIONS**, **Drug Interactions**).

In patients with epilepsy, mefloquine, especially when used in high doses, may increase the risk of convulsions. Therefore, in such patients, LARIAM should be used only for curative treatment and only if there are compelling medical reasons.

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels and a higher risk of adverse reactions (see **ACTION AND CLINICAL PHARMACOLOGY**, *Elimination* and **ADVERSE REACTIONS, Post Marketing Adverse Reactions**).

Mefloquine may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behaviour. 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. To minimize the chances of these adverse events, mefloquine should not be taken for prophylaxis in patients with active depression or with a history of psychiatric disturbances (including depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders).

In chemoprophylaxis the safety profile of mefloquine is characterized by a predominance of neuropsychiatric adverse reactions. If signs of acute anxiety, depression, restlessness or confusion occur during prophylactic use, 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.

Because of the long half-life of mefloquine, adverse reactions to LARIAM may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been

reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

Cases of agranulocytosis and aplastic anaemia have been reported during LARIAM therapy (see **ADVERSE REACTIONS**).

Geographical drug resistance patterns of P. falciparum occur and the preferred choice of malaria prophylaxis might be different from one area to another. 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 (see **ACTIONS AND CLINICAL PHARMACOLOGY**). For current advice on geographical resistance patterns competent national expert centers should be consulted.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Pregnancy:*

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. The safety of mefloquine use during the first trimester has not been established. Available data indicate that mefloquine is safe and effective in pregnancy beyond 16 weeks. Women of childbearing potential should be advised to practise contraception during malaria prophylaxis with LARIAM and for 3 months after the last dose. However, in the case of unplanned pregnancy, malaria prophylaxis with LARIAM 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 LARIAM falls within this range. No specific pattern of congenital malformations could be identified. For use of mefloquine during pregnancy, current national and international guidelines should be consulted.

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

## PRECAUTIONS

**General:**

As with most medications, hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted. Hypersensitivity reactions including anaphylaxis have been associated with the use of LARIAM (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, as dizziness or vertigo, a disturbed sense of balance and other disorders of the central or peripheral nervous system have been reported during and up to 3 weeks after the use of LARIAM. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of LARIAM (see **ADVERSE REACTIONS**, **Post Marketing Adverse Reactions**). 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 recommended.

LARIAM should be taken with caution in patients suffering from cardiac conduction disorders. 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 (see **WARNINGS** and **ADVERSE REACTIONS**). In patients with cardiac disease, the benefits of LARIAM therapy should be weighed against the possibility of adverse cardiac effects.

During clinical trials, this drug was not administered for longer than one year. If the drug is to be administered for a prolonged period, periodic evaluations including liver function tests should be performed, if feasible. 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) (see **TOXICOLOGY**). Therefore, periodic ophthalmic examinations are recommended.

**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 of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to an increase in mefloquine plasma concentrations and potential risk of adverse reactions. Therefore, mefloquine should be used with caution when administered concomitantly with CYP3A4 inhibitors. Similarly, inducers of the isoenzyme CYP3A4 may modify the pharmacokinetics/metabolism of mefloquine, leading to a decrease in mefloquine plasma concentrations.

*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 are not known to date.

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

Concomitant administration of LARIAM and other related antimalarial compounds (e.g., quinine, quinidine, chloroquine) may produce electrocardiographic abnormalities. If quinine or quinidine are to be used in the initial treatment of severe malaria, LARIAM 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, ß-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.

Halofantrine must not be administered with LARIAM therapy for prophylaxis or treatment of malaria or within 15 weeks of the last dose of LARIAM due to the risk of a potentially fatal prolongation of the QTc interval. There is evidence that the use of halofantrine during LARIAM therapy for prophylaxis or treatment of malaria or within 15 weeks after the last dose of LARIAM causes a significant lengthening of the QTc interval (see **WARNINGS**). Ketoconazole must not be administered with LARIAM therapy for prophylaxis or treatment of malaria or within 15 weeks of the last dose of LARIAM due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following coadministration (see **WARNINGS**).

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 LARIAM with quinine, quinidine or chloroquine may increase the risk of convulsions.

Patients taking LARIAM 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 LARIAM 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 LARIAM 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 LARIAM.

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 LARIAM (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 LARIAM on travellers receiving comedication, particularly diabetics or patients using anticoagulants, should be checked before departure.

*Impairment of Fertility:*

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) (see **TOXICOLOGY,** *Long-Term Toxicity*). Administration of 250 mg/week of mefloquine (base) to adult males for 22 weeks failed to reveal any deleterious effects on human spermatozoa.

*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 LARIAM is administered to a nursing woman. For use of mefloquine in nursing mothers current national and international guidelines should be consulted.

*Pediatric Use:*

Two studies were conducted to look at 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. The incidence of adverse reactions was higher than that observed in adults.

Experience with LARIAM in infants less than 3 months old or weighing less than 5 kg is limited. No relevant age-related changes have been observed in the pharmacokinetics of mefloquine.

*Geriatrics:*

No relevant age-related changes have been observed in the pharmacokinetics of mefloquine. Since electrocardiographic abnormalities have been observed in individuals treated with LARIAM and underlying cardiac disease is more prevalent in elderly than in younger patients, the benefits of LARIAM therapy should be weighed against the possibility of adverse cardiac effects in elderly patients (see **PRECAUTIONS**).

*Renal Insufficiency:*

No pharmacokinetic studies have been performed in patients with renal insufficiency since only a small proportion of the drug is eliminated renally.

*Hepatic Insufficiency:*

The pharmacokinetics of mefloquine in patients with compromised hepatic function have not been studied.

*Other:*

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

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

## ADVERSE REACTIONS

**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 LARIAM (mefloquine) for prophylaxis of malaria, the most frequently observed adverse experiences are nausea, vomiting, headache and dizziness. These

adverse events are generally mild and may decrease with prolonged use. In chemoprophylaxis the safety profile of mefloquine is characterized by a predominance of neuropsychiatric adverse reactions (see **WARNINGS** and **PRECAUTIONS**).

**Clinical Trial Adverse Drug Reactions:**

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, hair loss, emotional problems, pruritus, asthenia, transient emotional disturbances 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 **PRECAUTIONS**, **Drug Interactions**), and encephalopathy of unknown etiology during prophylactic mefloquine administration. The relationship of encephalopathy to drug administration could not be clearly established.

**Post Marketing Adverse Reactions:**

The most frequently reported adverse events are:

**Ear and Labyrinth Disorders:** vertigo.

**Gastrointestinal Disorders:** nausea, vomiting, loose stools or diarrhea and abdominal pain. These adverse events are generally mild and may decrease with prolonged use.

**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 anaemia (see **WARNINGS**).

**Cardiac Disorders:** tachycardia, palpitation, bradycardia, irregular heart rate, extrasystoles, other transient cardiac conduction alterations. Cases of AV-block have been reported.

Prolongation of the QTc interval has been reported during the use of mefloquine. The clinical significance of the QTc prolongation with the use of mefloquine remains undetermined (see **WARNINGS** and **PRECAUTIONS**).

**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 have been reported.

**Immune System Disorders:** cases of hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis have been reported.

**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). Cases of encephalopathy have been reported.

***Note:***

In the literature, the incidence of serious neuropsychiatric adverse drug reactions (eg. seizures, psychotic reactions) with LARIAM has been reported at 1/215 following treatment and 1/13,000 following prophylactic use.

**Psychiatric Disorders:** emotional problems (agitation, restlessness, anxiety, depression, mood swings, panic attacks, aggression, psychotic or paranoid reactions), confusional state, hallucinations (see **WARNINGS**).

There have been reports of suicidal ideations and suicide, but no relationship to drug administration has been established.

**Respiratory, Thoracic and Mediastinal Disorders:** dyspnea. Cases of pneumonitis of possible allergic etiology have been reported.

**Skin and Subcutaneous Tissue Disorders:** rash, exanthema, erythema, urticaria, pruritus, alopecia, hyperhidrosis. Cases of erythema multiforme and Stevens-Johnson syndrome have been reported.

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

Because of the long half-life of mefloquine, adverse reactions to LARIAM may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of LARIAM.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

**Symptoms and signs:**

In cases of overdosage with LARIAM, the symptoms mentioned under the **ADVERSE REACTIONS** section may be more pronounced.

**Treatment:**

Patients should be managed by symptomatic and supportive care following LARIAM overdose, particularly for cardiovascular disturbances. There are no specific antidotes. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Should diarrhea and/or vomiting occur, treat with standard fluid therapy.

## DOSAGE AND ADMINISTRATION

LARIAM (mefloquine) should be taken with food, and with at least one glass (240 mL) of liquid. 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.

**Prophylaxis:**

The recommended prophylactic dose of LARIAM 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 LARIAM 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 | ¾ tablet |
| > 20-30 | ½ tablet |
| 5 to 20 | ¼ tablet |

Experience with LARIAM 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.

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

When prophylaxis with LARIAM fails, physicians should carefully evaluate which antimalarial to use for therapy. 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 LARIAM tablets) while partially immune patients of the same weight should receive 750-1000 mg (3-4 LARIAM tablets). (See following table.)

Recommended total therapeutic dosages of LARIAM 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<br>1 tablet per 10 - 12 kg of weight | ¼ tablet per 4 kg of weight<br>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 LARIAM 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 LARIAM are at high risk of relapse because LARIAM does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse after initial treatment of the acute infection with LARIAM, patients should subsequently be treated with an 8-aminoquinoline (e.g. primaquine) in order to eliminate liver forms.

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

LARIAM 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.

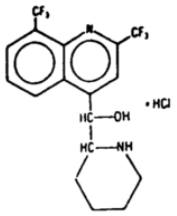
## PHARMACEUTICAL INFORMATION

Chemistry:

Tradename: LARIAM®

Proper Name: Mefloquine hydrochloride

Structural Formula:




Molecular Formula: $C_{17}H_{16}F_6N_2 \bullet HCl$

Molecular Weight: 414.79

Chemical Name: DL-erythro-2-piperidyl-2,8-bis(trifluoromethyl)-4-quinoline methanol hydrochloride.

*Description:* 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.

*Composition:* Each LARIAM 250 mg tablet contains 250 mg of mefloquine (base), present as mefloquine hydrochloride. The non-medicinal ingredients are ammonium-calcium alginate, cornstarch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer and talc.

*Storage:* Store at 15-30°C. The tablets are sensitive to moisture and should remain in their blister until consumed.

## AVAILABILITY OF DOSAGE FORMS

**Availability:**

LARIAM 250 mg tablets (containing 250 mg mefloquine base, present as mefloquine hydrochloride) are cross-scored (both sides), white, cylindrical, biplane tablets with bevelled edges imprinted ROCHE with hexagon on one side. Available in blister packages of 8 tablets.

**Disposal of unused/expired medicines:**
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

## INFORMATION FOR THE PATIENT

### LARIAM (Mefloquine) Tablets to Prevent Malaria

**This Information for the Patient guide is intended only for travellers who are taking LARIAM to prevent malaria.** The information may not apply to patients who are sick with malaria and who are taking LARIAM to treat malaria.

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

This document was revised in February 2009. Please read it before you start taking LARIAM and each time you get a refill. There may be new information. This document does not take the place of talking with your prescriber (doctor or other health care provider) about LARIAM and malaria prevention. Only you and your prescriber can decide if LARIAM is right for you. If you cannot take LARIAM you may be able to take a different medicine to prevent malaria.

### What is LARIAM?

LARIAM is the trade name for an antimalarial product containing the drug mefloquine.

Each LARIAM 250 mg tablet contains 250 mg of mefloquine (base) present as mefloquine hydrochloride. The non-medicinal ingredients are ammonium-calcium alginate, cornstarch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer and talc.

The tablets should be stored at 15-30°C. The tablets are sensitive to moisture and should remain in their blister until consumed.

### What is the most important information I should know about LARIAM?

**1. Take LARIAM exactly as prescribed to prevent malaria.**

Malaria is an infection that can cause death and is spread to humans through mosquito bites. If you travel to parts of the world where the mosquitoes carry the malaria parasite, you must take a malaria prevention medicine. LARIAM is one of a small number of medications approved to prevent and to treat malaria. If taken correctly, LARIAM is effective at preventing malaria but, like all medications, it may produce side effects in some patients.

**2. LARIAM can rarely cause serious mental problems in some patients.**

The most frequently reported side effects with LARIAM, such as nausea, difficulty sleeping, and bad dreams are usually mild and do not cause people to stop taking the medicine. However, people taking LARIAM occasionally experience severe anxiety, feelings that people are against them, hallucinations (seeing or hearing things that are not there for example), depression, unusual behavior, or feeling disoriented. There have been reports that in some patients these side effects continue after LARIAM is stopped. Some patients taking LARIAM think about killing themselves, and there have been rare reports of suicides. It is not known whether LARIAM was responsible for these suicides.

**If you use LARIAM to prevent malaria and you develop a sudden onset of unexplained anxiety, depression, restlessness or irritability, or confusion (possible signs of more serious mental problems), or you develop other serious side effects, including a persistently abnormal heart beat or palpitations, contact a doctor or health care provider. It may be necessary to stop taking LARIAM and use another malaria prevention medicine instead. If you can't get another medicine, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.**

**3. 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.**

Medicines approved in Canada for malaria prevention include 'LARIAM', doxycycline, atovaquone/proguanil, hydroxychloroquine, and chloroquine. Not all of these drugs work equally as well in all areas of the world where there is malaria. The chloroquines, for example, do not work in areas where the malaria parasite has developed resistance to chloroquine. LARIAM may be effective against malaria that is resistant to chloroquine or other drugs. All drugs used to prevent malaria have side effects that are different for each one. For example, some may make your skin more sensitive to sunlight (LARIAM does not do this).

**General Precautions with LARIAM:**

Do not take LARIAM to **prevent** malaria if you

- **have or had depression**
- **have had recent mental illness or problems**, including anxiety disorder, schizophrenia (a severe type of mental illness), or psychosis (losing touch with reality)
- **have or had seizures (epilepsy or convulsions)**
- **have rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or gloucose-galactose malabsorption**, as this product contains lactose
- **are allergic to quinine or quinidine (medicines related to LARIAM)**

**Tell your prescriber about all your medical conditions.** LARIAM may not be right for you if you have certain conditions, especially the ones listed below:

- **Heart Disease.** LARIAM may not be right for you.
- **Pregnancy.** Tell your prescriber if you are pregnant or plan to become pregnant. It is dangerous for the mother and for the unborn baby (fetus) to get malaria during pregnancy. Therefore, ask your prescriber if you should take LARIAM or another medicine to prevent malaria while you are pregnant.
- **Breast feeding.** LARIAM can pass through your milk and may harm the baby. Therefore, ask your prescriber whether you will need to stop breast feeding or use another medicine.
- **Liver problems.**

**Tell your prescriber about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.** This includes telling your doctor if you are taking anti-seizure medications such as valproic acid, carbamazepine, phenobarbital, and phenytoin. Some medicines may give you a higher chance of having serious side effects from LARIAM.

**How should I Take LARIAM?**

**Take LARIAM exactly as prescribed. If you are an adult or pediatric patient weighing 45 kg (99 pounds) or less, your prescriber will tell you the correct dose based on your weight.** There is limited information on the use of LARIAM in children less than 3 months old or weighing less than 5 kg.

**To Prevent Malaria**

- For adults and pediatric patients weighing over 45 kg, take 1 tablet of LARIAM at least 1 week before you travel to a malaria area (or 2 to 3 weeks before you travel to a malaria area, if instructed by your prescriber). This starts the prevention and also helps you see

how LARIAM affects you and the other medicines you take. **Take 1 LARIAM tablet once a week,** on the same day each week, while in a malaria area.

- **Continue taking LARIAM for 4 weeks after returning from a malaria area.** If you cannot continue taking LARIAM due to side effects or for other reasons, contact your prescriber.
- Take LARIAM just after a meal and with at least 1 cup (8 ounces) of water.
- If you miss taking a dose, take it as soon as you realize you have forgotten, and then take each remaining dose according to the dosage schedule, counting from the day that you took the missed dose.
- For children, LARIAM can be given with water or crushed and mixed with water or sugar water. The prescriber will tell you the correct dose for children based on the child's weight.
- If you are told by a doctor or other health care provider to stop taking LARIAM due to side effects or for other reasons, it will be necessary to take another malaria medicine. You must 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. If you don't have access to a doctor or other health care provider or to another medicine besides LARIAM and have to stop taking it, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.**

**What should I do in case of an overdose?**

| |
|---|
| In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms. |

**What should I avoid while taking LARIAM?**

- **Halofantrine (marketed under various brand names),** a medicine used to treat malaria. Taking both of these medications together, or taking halofantrine within 15 weeks after the last dose of LARIAM, can cause serious heart problems that can cause death.
- **Ketoconazole,** a medicine used to treat fungal infections. Taking both of these medications together, or taking ketoconazole within 15 weeks after the last dose of LARIAM, can cause serious heart problems that can cause death.
- **Do not become pregnant. Women should use effective birth control while taking LARIAM.**
- **Quinine, quinidine, or chloroquine (other medicines used to treat malaria).** Taking these medicines with LARIAM could cause changes in your heart rate or increase the risk of seizures.
- **Alcohol.** It is best to avoid alcoholic drinks during treatment with LARIAM.

In addition:

- **Be careful driving or in other activities** needing alertness and careful movements (fine motor coordination). LARIAM can cause dizziness or vertigo or loss of balance, even after you stop taking it.

- **Be aware that certain vaccines may not work if given while you are taking LARIAM.** Your prescriber may want you to finish taking your vaccines at least 3 days before starting LARIAM.

**What are the possible side effects of LARIAM?**

LARIAM, like all medicines, may cause side effects in some patients. The most frequently reported side effects with LARIAM when used for prevention of malaria include nausea, vomiting, diarrhea, dizziness, difficulty sleeping, and bad dreams. These are usually mild and do not cause people to stop taking the medicine.

In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

LARIAM may cause serious mental problems in some patients (see “What is the most important information I should know about LARIAM?”).

LARIAM may affect your liver and your eyes if you take it for a long time. Liver problems have occurred including liver failure, with symptoms of liver problems such as abdominal pain, nausea, vomiting, weakness and yellowing of the eyes and skin. Your prescriber will tell you if you should have your eyes and liver checked while taking LARIAM.

Blood problems such as aplastic anemia (bone marrow produces insufficient blood cells) and agranlocytosis (reduced white blood cells and neutrophils) have occurred with LARIAM.

**What else should I know about preventing malaria?**

- **Find out whether you need malaria prevention.** Before you travel, talk with your prescriber about your travel plans to determine whether you need to take medicine to prevent malaria. Even in those countries where malaria is present, there may be areas of the country that are free of malaria. In general, malaria is more common in rural (country) areas than in big cities, and it is more common during rainy seasons, when mosquitoes are most common. You can get information about the areas of the world where malaria occurs from Health Canada and from local authorities in the countries you visit. If possible, plan your travel to reduce the risk of malaria.
- **Take medicine to prevent malaria infection.** Without malaria prevention medicine, you have a higher risk of getting malaria. Malaria starts with flu-like symptoms, such as chills, fever, muscle pains, and headaches. However, malaria can make you very sick or cause death if you don’t seek medical help immediately. These symptoms may disappear for a while, and you may think you are well. But, the symptoms return later and then it may be too late for successful treatment.

  Malaria can cause confusion, coma, and seizures. It can cause kidney failure, breathing problems, and severe damage to red blood cells. However, malaria can be easily diagnosed with a blood test, and if caught in time, can be effectively treated.

  **If you get flu-like symptoms (chills, fever, muscle pains, or headaches) after you return from a malaria area,** get medical help right away and tell your health care provider that you may have been exposed to malaria.

  People who have lived for many years in areas with malaria may have some immunity to malaria (they do not get it as easily) and may not take malaria prevention medicine. This does not mean that you don’t need to take malaria prevention medicine.

- **Protect against mosquito bites.** Medicines do not always completely prevent your catching malaria from mosquito bites. So protect yourself very well against mosquitoes. Cover your skin with long sleeves and long pants, and use mosquito repellent and bed nets while in malaria areas. Ask your prescriber for other ways to protect yourself.

**General information about the safe and effective use of LARIAM**

Medicines are sometimes prescribed for conditions not listed in Information for the Patient guides. If you have any concerns about LARIAM, ask your prescriber. This Information for the Patient guide contains certain important information for travellers visiting areas with malaria. Your prescriber or pharmacist can give you information about LARIAM that was written for health care professionals. Do not use LARIAM for a condition for which it was not prescribed. Do not share LARIAM with other people.

**Disposal of unused/expired medicines:**

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

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Information wallet card to carry when you are taking LARIAM.

LARIAM® (mefloquine hydrochloride) Tablets - For Prevention of Malaria

You need to take malaria prevention medicine before you travel to a malaria area, while there, and after you leave a malaria area. If taken correctly, LARIAM is effective at preventing malaria, but like all medications, it may produce side effects in some patients. If you use LARIAM to prevent malaria and you develop a sudden onset of unexplained anxiety, depression, restlessness or irritability, or confusion (possible signs of more serious mental problems), or you develop other serious side effects, including a persistently abnormal heart beat or palpitations, contact a doctor or other health care provider. It may be necessary to stop taking LARIAM and use another malaria prevention medicine instead. If you can't get another medicine, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine. Other medicines approved in Canada for malaria prevention include: doxycycline, atovaquone/proguanil, hydroxychloroquine, and chloroquine. Not all malaria medicines work equally well in malaria areas.

Please read the Information for the Patient guide for additional information on LARIAM.

Revised: FEB/2009

(***French translation of the above on back side of wallet card)***

## PARASITOLOGY

### 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 | $ED_{50}$ (ng/mL) |
|---|---|
| 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 vivo 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 was 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 | 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 4.

**TABLE 4**

| 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 |
| sulfone 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.

## PHARMACOLOGY

### Preclinical Pharmacodynamics:

The intrinsic action of mefloquine on the cardiovascular system was examined in mouse and dog studies. Overall, mefloquine elicited dose-related hypotension. In the mouse study, a lethal intraperitoneal dose of 100 mg/kg caused transient hypertension that was followed by progressive hypotension. Intravenous administration of doses ranging from 1 to 20 mg/kg resulted in sharp dose-related hypotension. In the dog, a dose of 2.5 to 40 mg/kg given intravenously over a two-minute period resulted in hypotension. An IV bolus administration of doses ranging from 1 to 30 mg/kg induced transient hypotension.

Mefloquine alone, in combination with primaquine and in combination with propranolol was studied for its effect on cardiac automaticity in the dog. Mefloquine, given intravenously at 10 mg/kg, did not have an appreciable effect on blood pressure or on atrial and ventricular automaticity. Although mefloquine did not potentiate the effects of primaquine on atrial or ventricular automaticity, it did potentiate the effects of propranolol on atrial automaticity.

In the isolated dog heart perfused with autologous blood, direct effects of mefloquine were seen on the heart only at a high concentration of the drug, i.e., tenfold higher than achieved in vivo. These effects were believed to be the result of catecholamine release. In the mouse, mefloquine produced neither adverse effects on conduction of the cardiac impulse nor arrhythmias. However, it was shown that lethal doses could result in cardiac depression and hemolysis.

### Preclinical Pharmacokinetics:

Radiolabeled mefloquine is well absorbed in mice on oral administration (10 and 40 mg/kg, single doses) with peak levels occurring between 12 and 24 hours and a plasma half-life of 48 hours. In mouse feces, there were three peaks (one similar to the parent drug) and the urine showed three similar peaks, plus two additional small peaks.

Rhesus monkeys given a single oral dose of 10 mg/kg, excreted about half of the radioactivity in the urine and 30% in the feces. It is believed that extensive enterohepatic circulation occurs in monkeys.

Mefloquine inhibited some nonspecific esterases and three oxidative hepatic microsomal enzymes, in the rat, and thus interferes with these enzymatic pathways.

**Clinical Pharmacology** (see **ACTIONS AND CLINICAL PHARMACOLOGY**)

## TOXICOLOGY

### Acute Toxicity

| Species | Sex | Route | LD50 (mg/kg; 95% CL) | 14-Day Observations |
|---|---|---|---|---|
| Mice | F | p.o.<br>i.p. | 1320 (1213-1436)<br>58 (50-68) | Most deaths in 4-7 days; difficulty breathing, slight ataxia, rough hair coat, weight loss. |
| | M | p.o.<br>i.p.<br>p.o.* | 1443 (1275-1598)<br>44 (36-51)<br>810 (653-1004) | Toxic signs before death included: lethargy, prostration, rough hair, difficulty breathing. |
| Rats | M | p.o<br>i.p.<br>p.o.*<br>i.p.* | 773 (734-819)<br>63 (54-71)<br>880 (807-959)<br>130 (114-148) | * Most deaths occurred in first week after p.o. and first day after i.p. administration. |
| Guinea pigs | M | p.o.*<br>i.p.* | 275 (216-351)<br>70 (61-80) | |

Note: The active material was suspended in tap water or in saline in 0.2% methylcellulose and 0.4% Tween 80 (MTS).

Groups of two male and two female beagle dogs received oral administration of single doses of mefloquine suspended in methylcellulose:Tween 80:water at 0, 6, 13.5, 30 or 68 mg/kg. Occasional slight emesis occurred in one or two dogs. An increase in the SGPT values was also noted.

In another study where beagle dogs received single oral doses of mefloquine at 120 or 420 mg/kg in capsule forms, no toxic effects were noted.

Long-Term Toxicity

| ANIMAL SPECIES AND STUDY DURATION | DOSE AND ROUTE OF ADMINISTRATION (MG/KG/DAY) | OBSERVATIONS |
|---|---|---|
| **SUBACTUE AND SUBCHRONIC TOXICITY STUDIES** | | |
| Albino CD®<br>Sprague-Dawley Rats<br>6M/group<br>28 days | 0, 5, 30 or 150<br>p.o.<br>(gastric intubation) | - High Dose Group: six rats died or were necropsied before their death during the second week of treatment; became inactive, showed rough fur coat, lost appetite; lost weight during second week and were depleted of body fat; elevated SGPT and BUN levels; increase in neutrophils; decrease in lymphocytes; lesions were seen in the myocardium, skeletal muscle and lymphoid tissues; relative liver, adrenal, thyroid and testicle weight were significantly increased (due to severe loss of body weight).<br>- Mid Dose: increases were noted in red blood cells, hematocrit, hemoglobin concentration, neutrophil percentage; lymphocyte percentage was decreased. |
| Beagle Dogs<br>2/sex/group<br>28 days | 0, 5, 30 or 150<br>p.o.<br>(capsules) | - High Dose Group: 3 of 4 dogs died or were moribund during the 3rd to 4th week, prior to death dogs were unresponsive, ataxic and one dog had convulsions. Persistent diarrhea; occasional emesis; weight loss; decreased reticulocytes and lymphocytes; increased neutrophils and leukocytes; elevated SGOT/AST, SGPT/ALT, BUN and alkaline phosphatase values with corresponding tissue lesions were noted; increased liver and kidney weights and decreased spleen weights.<br>- Mid Dose: Occasional diarrhea, emesis and lesions in lymphoid and/or liver tissue; punch out holes or starry-sky effects in the germinal centres of the tonsil and/or lymph nodes. |
| Beagle Dogs<br>2/sex/group<br>28 days | 0, 6, 13.5, 30 or 68 of either mefloquine (MQ) or the threo diastereomer (DSM)<br>p.o.<br>(intragastric intubation) | - Four dogs in DSM high dose group died.<br>- High Dose Group: emesis; mild diarrhea; salivation; weight loss; elevated relative liver and adrenal weight; increased BUN levels; degenerative liver changes; lymphoid atrophy in tonsils; thymus and peripheral lymph nodes.<br>- Weight gain was slightly depressed at 30 mg/kg/day. |

| ANIMAL SPECIES AND STUDY DURATION | DOSE AND ROUTE OF ADMINISTRATION (MG/KG/DAY) | OBSERVATIONS |
|---|---|---|
| Beagle Dogs<br>4M/group<br>91 days | 0, 13.5, 30 or 68<br>p.o.<br>(intragastric intubation) | - High Dose Group: one dog died; clonic-tonic convulsions with repeated opisthotonus (n=1); elevated SGPT/ALT, SGOT/AST, BUN, lactic dehydrogenase, alpha-hydroxybutyric dehydrogenase; hepatic lesions; portal inflammation and/or bile duct hyperplasia and minimal-moderate necrosis of the adrenal gland.<br>- High and Mid Dose: emesis; diarrhea and/or soft stool; elevated alkaline phosphatase levels; increased relative liver weight; weight loss; lymphoid depletion involving the lymph nodes,thymus, tonsil, stomach and small intestine; fundus changes characterized primarily by pigment aggregation in the retina observed in one dog; cloudiness of the ocular lens observed in all dogs. |
| Rhesus Monkeys<br>2/sex/group<br>90 days | 0, 13.5, 30 or 68<br>p.o.<br>(intragastric intubation) | - High and Mid-Dose: significant increase in liver weight; increased heart weights; lower testicular weights. |
| **CHRONIC TOXICITY STUDIES** | | |
| $BDF_1$ (C57B1 x DBA) Mice<br>52/sex/treated group<br>100/sex/control<br>2 years | 0, 5, 12.5, 30<br>p.o.<br>(in diet) | - High Dose: male mice had decreased body weight compared to control mice (observation noted at week 44 until study completion); females had an increased incidence of unscheduled deaths (primarily in last two months of study); decreased leukocytic infiltration of the liver (not dose related) and gastric mucosal hyperplasia; gastritis noted in both sexes.<br>- Statistical significant increase in hepatomas in mid dose male mice (14%), controls (1%) and low dose mice (8%). |
| Albino CD® Rats<br>15M/group<br>52 weeks | 0, 5, 25, 125<br>mg/kg/wk<br>p.o. | - High Dose Group: degree of pneumonia slightly more severe than other dose groups, one rat developed a tumor under the skin of the neck at the 34th week.<br>- Body weights of rats receiving 25 and 125 mg/kg/wk were significantly smaller than the control rats at various periods throughout the study. |

| ANIMAL SPECIES AND STUDY DURATION | DOSE AND ROUTE OF ADMINISTRATION (MG/KG/DAY) | OBSERVATIONS |
|---|---|---|
| Long Evans Hooded Rats<br>70/sex/treated group<br>120/sex/control<br>2 years | 0, 5, 12.5, 30<br>p.o.<br>(in diet) | - High Dose Group: weight gain of both sexes significantly depressed; increased incidence of spontaneous death among both sexes; males had decreased testicle size and paralysis of hind limbs; females showed increased vaginal hemorrhage, cystic ovaries and distended uteri filled with fluid; elevated SGOT/AST and BUN levels (male and female); at study completion, both sexes showed lesions in eye, lung, kidney, reproductive organs, skeletal muscle, spleen and lymph node.<br>- Mid and High Dose: retinal degeneration, opacity of the lens and/or retinal edema in both sexes (severity was dose related and occurrence was greater in females).<br>- Mid Dose Group: mild lesions of reproductive organs and bile duct hyperplasia<br>- Low Dose Group: lesions in the epididymis and prostate (M); epithelial vacuolization of epididymis, foamy macrophages in lungs and skeletal muscle degeneration. |
| Beagle Dogs<br>4/sex/group<br>52 weeks | 0, 5, 25, 125<br>mg/kg/wk<br>p.o.<br>(capsules) | - Larger absolute and relative adrenal weights in high dose group compared with controls. |

| ANIMAL SPECIES AND STUDY DURATION | DOSE AND ROUTE OF ADMINISTRATION (MG/KG/DAY) | OBSERVATIONS |
|---|---|---|
| **FERTILITY AND GENERAL REPRODUCTIVE PERFORMANCE** | | |
| Albino CD® Rats<br>24F/group<br>Rats received mefloquine 21 days before mating until post-partum day 21 | 0, 5, 20, 50<br>p.o.<br>(in diet) | - High Dose Group: reduced feed consumptions; reduced growth observed in pups (possibly related to the reduced feed consumption); reduced implant viability index and viability index during lactation; reduced litter size (also noted in mid dose group). |
| Weanling Albino CD® Rats<br>20M/group<br>Rats received mefloquine for 13 weeks before mating with untreated females | 0, 5, 20, 50<br>p.o.<br>(in diet) | - High Dose Group: reduction in body weight; decreased erythrocyte count, hematocrit, hemoglobin concentration; increased reticulocyte counts, neutrophil percentage; decreased lymphocyte percentage; elevated SGOT/AST levels; reduced ratio of pregnant to sperm-positive females; reduced number of viable litters; reduced fertility index.<br>- Lesions in the epididymis of male rats (mid and high dose groups). |
| Albino CD® Rats<br>40M/low dose<br>80M/control and high dose<br>13 to 16 weeks with a subsequent recovery period (13 or 31 weeks) | 0, 19.1, 46<br>p.o.<br>(in diet) | - High Dose Group: 5/80 died between the 9th and 12th week of treatment, 6/20 died during the mating period (weeks 13-16); reduced weight gain during the treatment period (weight returned to normal during recovery period); failure of rats to impregnate untreated females at the end of the treatment period; lesions in reproductive organs primarily in the epididymides and/or ductulus efferents; atrophy and vacuolar degeneration of the epithelium in the prostate and seminal vesicle.<br>- Low Dose Group: reduced fertility index observed in rats after 13-week recovery period (returned to normal after a recovery period of 31 weeks); lesions similar to high dose, but were reversible in recovery periods. |
| **TERATOLOGY** | | |
| Albino CD® Rats<br>20 pregnant rats/group<br>Days 6 to 15 of gestation | 0, 10, 20 or 100<br>p.o.<br>(intragastric intubation) | - High Dose Group: 11 of 26 treated died between gestational days 11 and 20; rats grew slower and consumed less feed than control rats (consumed 89% as much feed as control group, but gained only 57% as much weight); fetuses had reduced body weight, reduced crown-rump length, increased incidence of serious external, soft tissue and skeletal defects; domed craniums occurred at a high rate, high incidence of hydrocephalus; malformed interparietals, incompletely ossified supra occipitals, and incompletely ossified skull bones. |

| ANIMAL SPECIES AND STUDY DURATION | DOSE AND ROUTE OF ADMINISTRATION (MG/KG/DAY) | OBSERVATIONS |
|---|---|---|
| Füllinsdorf Albino Rats<br>40 pregnant rats/group | 0, 100, 250 or 500 — gestation day 7.<br>0, 50, 125 or 250 — gestation days 10 and 13<br>p.o.<br>(stomach tube) | - 38/40 rats died in the high dose groups (500/250 mg/kg).<br>- 250/125 mg/kg: slight reduction of the weight gain. |
| Albino CD®-1 Mice<br>15-20 pregnant mice/group | 0, 10, 20, 100 or 200 gestation days 6-15.<br>150 gestation days 9-11 or days 12-14<br>p.o.<br>(intragastric intubation) | - High Dose Group (200): increased mortality, reduced feed consumption, reduced growth (adults).<br>- Fetal growth reduced at 100, 150 and 200 mg/kg administered during organogenesis and 150 mg/kg administered from gestational days 9-11 (reduced growth in 200 mg/kg may be due to malnourishment of dams).<br>- Cleft palate in fetuses from dams (100 mg/kg and greater).<br>- ≥ 100: fetal growth reduced; cleft palate in fetuses. |
| Füllinsdorf Albino Mice<br>40 pregnant mice/group | 0, 80, 160 or 400 — day 7 of gestation.<br>0, 40, 80 or 200 days 9, 11, 13 and 15 of gestation<br>p.o.<br>(stomach tube) | - Deaths occurred in mice receiving 160/80 (3/40) and 400/200 mg/kg (10/40).<br>- 160/80 mg/kg Dose Group: decrease in body weight of fetuses; cleft palate (1); hiatus hernia (1); slight enlargement of third cerebral ventricle (1).<br>- 400/200 mg/kg Dose Group: decrease in body weight of fetuses; cleft palate (5); exencephaly (2). |

| ANIMAL SPECIES AND STUDY DURATION | DOSE AND ROUTE OF ADMINISTRATION (MG/KG/DAY) | OBSERVATIONS |
|---|---|---|
| Füllinsdorf Swiss Hare Rabbits<br>19 or 20 pregnant rabbits/group | 0, 30, 80 or 160 — day 7 of gestation<br>0, 15, 40 or 80 — days 10, 13 and 16 of gestation<br>p.o.<br>(stomach tube) | - Weight gain slightly reduced in all treatment groups.<br>- Two rabbits died in the highest dose groups (160/80 mg/kg) of unknown cause.<br>- Resorption rate in high dose groups (160/80 mg/kg) was 41.1%; middle dose groups (80/40 mg/kg) resorption rate was 33.8%.<br>- One fetus with slightly enlarged fourth ventricle and two fetuses with ectopia observed in high dose groups.<br>- Two and three fetuses with partly missing medulla oblongata in the high and middle dose groups, respectively.<br>- Survival rate of pups was 64.8 and 81.4% in the high and middle dose groups respectively. |
| *Füllinsdorf Swiss Hare Rabbits<br>20 pregnant rabbits/group | 0 or 80 — gestation days 7.<br>0 or 40 — gestation days 10, 13 and 16<br>p.o.<br>(stomach tube) | - Earlier findings of partly missing medulla oblongata were not found. |
| **PERI/POSTNATAL STUDY IN RATS** | | |
| Albino CD® Rats<br>20 pregnant rats/group<br>Gestation day 16 through lactation day 21 | 0, 7, 17-44 or 70<br>p.o.<br>(in diet) | - <u>High Dose Group</u>: 2 of 16 dams died (postnatal period); postnatal weight of dams reduced (may be related to reduced feed consumption); pup growth reduced and no offspring survived until day 21.<br>- Drug related effects on offspring were determined to be produced during the postnatal treatment period. |

**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:**

*Immunology:*

Two separate studies were performed in mice to determine the effect of mefloquine on the immune system.

a) Groups of two mice received oral 150 mg/kg mefloquine for five days. No significant effect on antibody formation was noted.

b) Two groups of mice (10/group tested for IgM and 5/group for IgG) received intraperitoneal doses of mefloquine at 0, 10 or 40 mg/kg. Death occurred in 11 of 49 mice in one week at the high dose. Increased phagocytic function was seen at 10 mg/kg, but not at 40 mg/kg. Significant depression of a delayed hypersensitivity reaction occurred.

*Ophthalmology:*

a) Groups of four female albino mice received phenobarbital i.p. at 100 mg/kg for three days followed by a single oral dose of mefloquine at 810 mg/kg. An opaque area was seen in the posterior portion of both eyes in one mouse and in the right eye of another mouse. The visual and microscopic lesions seen were unlikely to have been induced by mefloquine.

b) Groups of 20 female albino mice received phenobarbital i.p. at 100 mg/kg for three days followed by a single oral dose of mefloquine at 810 mg/kg. Female CD-1 mice had unilateral opacities. Mefloquine did not cause or alter the pre-existing eye abnormality.

*Phototoxicity:*

a) Groups of four albino mice received mefloquine i.p. at 0, 20, 25 or 50 mg/kg, s.c. at 0, 300 or 600 mg/kg and p.o. at 0, 50, 100 or 200 mg/kg. Mefloquine had little or no phototoxic effect after a 70-hour exposure period to long-wavelength UV radiation.

b) Groups of two white swine received four oral doses of mefloquine at 0, 25 or 50 mg/kg during 44 hours of irradiation and ten oral doses at 0, 15 or 25 mg/kg during ten days of irradiation. Mefloquine did not elicit a phototoxic reaction in white swine. However, four doses of 50 mg/kg during 44 hours of irradiation produced incoordination, convulsions and death. There was no evidence of abnormal hematologic or biochemical blood values or gross microscopic lesions at 15 or 25 mg/kg for ten days.

*Comparison of Toxic Effects with Juvenile and Adult Rats:*

Groups of 12 albino juvenile male rats and 12 albino juvenile female rats received mefloquine p.o. five times a week for five weeks at 0, 30, 90 or 150 mg/kg. Groups of four albino adult male rats and four albino adult female rats received mefloquine p.o. five times a week for six weeks at 0, 30, 90 or 150 mg/kg. No significant difference of incidence or type of toxic signs were seen between juveniles and adults. However, deaths were 20 to 30% lower in juveniles and their body weight development was better than the adults.

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