CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 019591/S-014&017

Trade Name:	Lariam for oral use, 250mg
Generic or Proper Name:	Mefloquine Hydrochloride
Sponsor:	Hoffman-LaRoche, Inc.
Approval Date:	January 10, 2003
Indication:	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 *Plasmodium vivax*.

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NDA 019591/S-014&017

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APPLICATION NUMBER:

NDA 019591/S-014&017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-014, S-017

Hoffman-LaRoche, Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug applications dated August 19, 1999 and November 6, 2000, received August 24, 1999 and November 8, 2000, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

We acknowledge receipt of your submissions dated December 2, 2002 and December 19, 2002.

These supplemental new drug applications provide for the following changes to the Lariam® package insert. Added text is noted by double underline and deleted text is noted by ~~strikethrough~~:

1. CLINICAL PHARMACOLOGY

• A **Pharmacokinetic** subsection was added with subheadings to read:

~~Pharmacokinetic studies of mefloquine in healthy male subjects showed that a significant lagtime occurred after drug administration, and the terminal elimination half-life varied widely (13 to 24 days) with a mean of about 3 weeks. Mefloquine is a mixture of enantiomeric molecules whose rates of release, absorption, transport, action, degradation and elimination may differ. A valid pharmacokinetic model may not exist in such a case.~~

~~Additional studies in European subjects showed slightly greater concentrations of drug for longer periods of time. The absorption half-life was 0.36 to 2 hours, and the terminal elimination half-life was 15 to 33 days. The primary metabolite was identified and its concentrations were found to surpass the concentrations of mefloquine.~~

~~Multiple-dose kinetic studies confirmed the long elimination half-lives previously observed. The mean metabolite to mefloquine ratio measured at steady-state was found to range between 2.3 and 8.6.~~

~~The total clearance of the drug, which is essentially all hepatic, is approximately 30 mL/min. The volume of distribution, approximately 20 L/kg, indicates extensive distribution. The drug is highly~~

~~bound (98%) to plasma proteins and concentrated in blood erythrocytes, the target cells in malaria, at a relatively constant erythrocyte to plasma concentration ratio of about 2.~~

~~The pharmacokinetics of mefloquine in patients with compromised renal function and compromised hepatic function have not been studied.~~__Pharmacokinetics__

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formation 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. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, 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). In healthy volunteers, a dose of 250 mg once weekly, produces maximum steady-state plasma concentrations of 1000 to 2000 µg/L, which are reached after 7 to 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. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes, was found to be reversible. Protein binding is about 98%.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see **PRECAUTIONS: Nursing Mothers**).

Metabolism

Two metabolites have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P. falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations, 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 under steady-state condition accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine.

Pharmacokinetics in Special Clinical Situations

Children and the Elderly

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.

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. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy persons.

Although clearance of mefloquine may increase in late pregnancy, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

The pharmacokinetics of mefloquine may be altered in acute malaria.

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.

During long-term prophylaxis (>2 years), the trough concentrations and the elimination half-life of mefloquine were similar to those obtained in the same population after 6 months of drug use, which is when they reached steady state.

In vitro and in vivo studies showed no hemolysis associated with glucose-6-phosphate dehydrogenase deficiency (see **ANIMAL TOXICOLOGY**).

- A **Microbiology** subsection was added with subheadings to read:

~~***Microbiology:*** **Strains of Plasmodium falciparum resistant to mefloquine have been reported.**~~

Microbiology

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

Mefloquine is active against the erythrocytic stages of *Plasmodium* species (see **INDICATIONS AND USAGE**). However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see **INDICATIONS AND USAGE**).

Drug Resistance

Strains of *Plasmodium falciparum* with decreased susceptibility to mefloquine can be selected in vitro or in vivo. Resistance of *P. falciparum* to mefloquine has been reported, in areas of multi-

drug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

Cross Resistance

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

2. CONTRAINDICATIONS

The first sentence in this section was revised to read:

Use of Lariam is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds (eg, quinine and quinidine) or to any of the excipients contained in the formulation.

3. PRECAUTIONS

- The first two paragraphs in the **General** subsection were revised to read;:

General

Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.

~~***General:***~~ In patients with epilepsy, Lariam may increase the risk of convulsions. The drug should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see **PRECAUTIONS: Drug Interactions**).

Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving, piloting aircraft, operating machinery, and deep-sea diving, as dizziness, a loss of balance, or other disorders of the central or peripheral nervous system have been reported during and following the use of Lariam. These effects may occur after therapy is discontinued due to the long half-life of the drug. Lariam should be used with caution in patients with psychiatric disturbances because mefloquine use has been associated with emotional disturbances (see **ADVERSE REACTIONS**).

- The fourth bullet in the **Information for Patients** subsection was revised to read:

  - that when used as prophylaxis, the first dose of Lariam should be taken 1 week prior to ~~departure~~ arrival in an endemic area;

- The second paragraph in the **Drug Interactions** subsection was revised to read:

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine ~~should~~ must not be given simultaneously with or subsequent to Lariam (see **WARNINGS**).

- The seventh paragraph in the **Drug Interactions** subsection was revised to read:

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving comedication, particularly ~~those on coagulants or antidiabetics~~ diabetics or patients using anticoagulants, should be checked before departure.

- The following statements were added to the end of the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, **Pregnancy, Teratogenic Effects** statement:

Women of childbearing potential should also be advised to practice contraception during malaria prophylaxis with Lariam and up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination.

- The following phrase was added to the first sentence in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, **Nursing Mothers** statement:

Mefloquine is excreted in human milk in small amounts, the activity of which is unknown.

- A **Geriatric Use** subsection was added to the end of this section to read:

Geriatric Use
Clinical studies of Lariam did not include sufficient numbers of subjects aged 65 and over 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 Lariam (see **PRECAUTIONS**) 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.

4. ADVERSE REACTIONS

- A subsection was added to the reference in the first sentence of the fourth paragraph to read:

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.

5. OVERDOSAGE

- This section was revised to read:

In cases of overdosage with Lariam, the symptoms mentioned under **ADVERSE REACTIONS** may be more pronounced. The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate. Monitor cardiac function (if possible by ECG) and neuro~~logic and~~ psychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances. ~~Treat vomiting or diarrhea with standard fluid therapy.~~

6. DOSAGE AND ADMINISTRATION (see INDICATIONS AND USAGE)

- The **Adult Patients** subsection was revised to read:

Treatment of mild to moderate malaria in adults caused by P. vivax or mefloquine-susceptible strains of P. falciparum

Five tablets (1250 mg) mefloquine hydrochloride to be given as a single oral dose. The drug should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

If a full-treatment course ~~has been administered without clinical cure, alternative treatment should be given~~ with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

Note: 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 derivative (eg, primaquine).

Malaria Prophylaxis

One 250 mg Lariam tablet once weekly.

Prophylactic drug administration should begin 1 week before ~~departure to~~ arrival in an endemic area. Subsequent weekly doses should ~~always~~ be taken regularly, always on the same day of ~~the~~ each week, preferably after the main meal. To reduce the risk of malaria after leaving an endemic area, prophylaxis ~~should~~ must be continued for 4 additional weeks to ensure suppressive blood levels of the drug when merozoites emerge from the liver. Tablets should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

In certain cases, eg, when a traveler is taking other medication, it may be desirable to start prophylaxis 2 to 3 weeks prior to departure, in order to ensure that the combination of drugs is well tolerated (see **PRECAUTIONS: Drug Interactions**).

When prophylaxis with Lariam fails, physicians should carefully evaluate which antimalarial to use for therapy.

- The **Pediatric Patients** subsection was revised to read:

Treatment of mild to moderate malaria in pediatric patients caused by mefloquine-susceptible strains of P. falciparum

Twenty (20) to 25 mg/kg ~~for non immune patients~~ body weight. Splitting the total ~~curative~~ therapeutic dose into 2 doses taken 6 to 8 hours apart may reduce the occurrence or severity of adverse effects. Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. ~~For very young patients, the dose may be crushed, mixed with water or sugar water and may be administered via an oral syringe.~~

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.

If a full-treatment course ~~has been administered without clinical cure, alternative treatment should be given~~ with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

In pediatric patients, the administration of Lariam for the treatment of malaria has been associated with early vomiting. In some cases, early vomiting has been cited as a possible cause of treatment failure (see **PRECAUTIONS**). If a significant loss of drug product is observed or suspected because of vomiting, a second full dose of Lariam should be administered to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30 to 60 minutes after a dose, an additional half-dose should be given. If vomiting recurs, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time.

The safety and effectiveness of Lariam to treat malaria in pediatric patients below the age of 6 months have not been established.

Malaria Prophylaxis

The following doses have been extrapolated from the recommended adult dose. Neither the pharmacokinetics, nor the clinical efficacy of these doses have been determined in children owing to the difficulty of acquiring this information in pediatric subjects. The recommended prophylactic dose of Lariam is ~~3 to~~ approximately 5 mg/kg body weight once weekly. One 250 mg Lariam tablet should be taken once weekly in pediatric patients weighing over 45 kg. In pediatric patients weighing less than 45 kg, the weekly dose decreases in proportion to body weight:

30 to 45 kg:	¾ tablet
20 to 30 kg:	½ tablet
~~up~~ 10 to 20 kg:	¼ tablet
5 to 10 kg:	tablet*

*Approximate tablet fraction based on a dosage of 5 mg/kg body weight. Exact doses for children weighing less than 10 kg may best be prepared and dispensed by pharmacists.

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

7. **HOW SUPPLIED**

The last sentence in this section was revised to read:

Tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use

as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter:

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 19-591/S-014, S-017." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

1/10/03 02:21:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-014&017

LABELING

LARIAM®

brand of

mefloquine hydrochloride

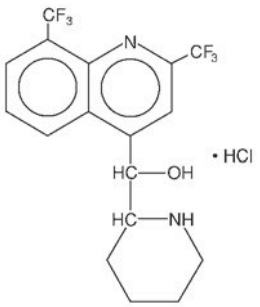
TABLETS

DESCRIPTION

Lariam (mefloquine hydrochloride) is an antimalarial agent available as 250-mg tablets of mefloquine hydrochloride (equivalent to 228.0 mg of the free base) for oral administration.

Mefloquine hydrochloride is a 4-quinolinemethanol derivative with the specific chemical name of (R*, S*)-(±)-α-2-piperidinyl-2,8-bis (trifluoromethyl)-4-quinolinemethanol hydrochloride. It is a 2-aryl substituted chemical structural analog of quinine. The drug is a white to almost white crystalline compound, slightly soluble in water.

Mefloquine hydrochloride has a calculated molecular weight of 414.78 and the following structural formula:



The inactive ingredients are ammonium-calcium alginate, corn starch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer #331, and talc.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formation 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. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, 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). In healthy volunteers, a dose of 250 mg once weekly, produces maximum steady-state plasma concentrations of 1000 to 2000 µg/L, which are reached after 7 to 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. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes, was found to be reversible. Protein binding is about 98%.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see **PRECAUTIONS: Nursing Mothers**).

Metabolism

Two metabolites have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P. falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations, 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 under steady-state condition accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine.

Pharmacokinetics in Special Clinical Situations

Children and the Elderly

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.

LARIAM® (mefloquine hydrochloride)

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. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy persons.

Although clearance of mefloquine may increase in late pregnancy, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

The pharmacokinetics of mefloquine may be altered in acute malaria.

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.

During long-term prophylaxis (>2 years), the trough concentrations and the elimination half-life of mefloquine were similar to those obtained in the same population after 6 months of drug use, which is when they reached steady state.

In vitro and in vivo studies showed no hemolysis associated with glucose-6-phosphate dehydrogenase deficiency (see **ANIMAL TOXICOLOGY**).

Microbiology

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

Mefloquine is active against the erythrocytic stages of *Plasmodium* species (see **INDICATIONS AND USAGE**). However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see **INDICATIONS AND USAGE**).

Drug Resistance

Strains of *Plasmodium falciparum* with decreased susceptibility to mefloquine can be selected in vitro or in vivo. Resistance of *P. falciparum* to mefloquine has been reported, in areas of multi-drug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

Cross Resistance

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

LARIAM® (mefloquine hydrochloride)

INDICATIONS AND USAGE

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 *Plasmodium vivax*. There are insufficient clinical data to document the effect of mefloquine in malaria caused by *P. ovale* or *P. malariae.*

> *Note:* 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 (eg, primaquine).

Prevention of Malaria

Lariam is indicated for the prophylaxis of *P. falciparum* and *P. vivax* malaria infections, including prophylaxis of chloroquine-resistant strains of *P. falciparum*.

CONTRAINDICATIONS

Use of Lariam is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds (eg, quinine and quinidine) or to any of the excipients contained in the formulation. Lariam should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders, or with a history of convulsions.

WARNINGS

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 to complete the course of therapy.

Data on the use of halofantrine subsequent to administration of Lariam suggest a significant, potentially fatal prolongation of the QTc interval of the ECG. Therefore, halofantrine must not be given simultaneously with or subsequent to Lariam. No data are available on the use of Lariam after halofantrine (see PRECAUTIONS: Drug Interactions).

Mefloquine may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior. 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 recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders. Lariam should be used with caution in patients with a previous history of depression.

During prophylactic use, if psychiatric symptoms such as 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.

Concomitant administration of Lariam and quinine or quinidine may produce electrocardiographic abnormalities.

Concomitant administration of Lariam and quinine or chloroquine may increase the risk of convulsions.

PRECAUTIONS

General

Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.

In patients with epilepsy, Lariam may increase the risk of convulsions. The drug should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see **PRECAUTIONS: Drug Interactions**).

Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving, piloting aircraft, operating machinery, and deep-sea diving, as dizziness, a loss of balance, or other disorders of the central or peripheral nervous system have been reported during and following the use of Lariam. These effects may occur after therapy is discontinued due to the long half-life of the drug. Lariam should be used with caution in patients with psychiatric disturbances because mefloquine use has been associated with emotional disturbances (see **ADVERSE REACTIONS**).

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels.

This drug has been administered for longer than 1 year. If the drug 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) (see **ANIMAL TOXICOLOGY**). Therefore, periodic ophthalmic examinations are recommended.

LARIAM® (mefloquine hydrochloride)

Parenteral studies in animals show that mefloquine, a myocardial depressant, possesses 20% of the antifibrillatory 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 also cardiovascular effects under **PRECAUTIONS: Drug Interactions** and **ADVERSE REACTIONS**). The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Laboratory Tests

Periodic evaluation of hepatic function should be performed during prolonged prophylaxis.

Information for Patients

Patients should be advised:

- that malaria can be a life-threatening infection in the traveler;
- that Lariam is being prescribed to help prevent or treat this serious infection;
- that in a small percentage of cases, patients are unable to take this medication because of side effects, and it may be necessary to change medications;
- that when used as prophylaxis, the first dose of Lariam should be taken 1 week prior to arrival in an endemic area;
- that if the patients experience psychiatric symptoms such as acute anxiety, depression, restlessness or confusion, 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;
- that no chemoprophylactic regimen is 100% effective, and protective clothing, insect repellents, and bednets are important components of malaria prophylaxis;
- to seek medical attention for any febrile illness that occurs after return from a malarious area and to inform their physician that they may have been exposed to malaria.

Drug Interactions

Drug-drug interactions with Lariam have not been explored in detail. There is one report of cardiopulmonary arrest, with full recovery, in a patient who was taking a beta blocker (propranolol) (see **PRECAUTIONS: General**). The

effects of mefloquine on the compromised cardiovascular system have not been evaluated. The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine must not be given simultaneously with or subsequent to Lariam (see **WARNINGS**).

Concomitant administration of Lariam and other related compounds (eg, quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions (see **WARNINGS**). If these drugs are to be used in the initial treatment of severe malaria, Lariam administration should be delayed at least 12 hours after the last dose. There is evidence that the use of halofantrine after mefloquine causes a significant lengthening of the QTc interval. Clinically significant QTc prolongation has not been found with mefloquine alone.

This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically, coadministration of other drugs known to alter cardiac conduction (eg, anti-arrhythmic or beta-adrenergic blocking agents, calcium channel blockers, antihistamines or H_1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval. There are no data that conclusively establish whether the concomitant administration of mefloquine and the above listed agents has an effect on cardiac function.

In patients taking an anticonvulsant (eg, valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of Lariam may reduce seizure control by lowering the plasma levels of the anticonvulsant. Therefore, patients concurrently taking antiseizure medication and Lariam should have the blood level of their antiseizure medication monitored and the dosage adjusted appropriately (see **PRECAUTIONS: General**).

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 3 days before the first dose of Lariam.

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving comedication, particularly diabetics or patients using anticoagulants, should be checked before departure.

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

LARIAM® (mefloquine hydrochloride)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of mefloquine was studied in rats and mice in 2-year feeding studies at doses of up to 30 mg/kg/day. No treatment-related increases in tumors of any type were noted.

Mutagenesis

The mutagenic potential of mefloquine was studied in a variety of assay systems including: Ames test, a host-mediated assay in mice, fluctuation tests and a mouse micronucleus assay. Several of these assays were performed with and without prior metabolic activation. In no instance was evidence obtained for the mutagenicity of mefloquine.

Impairment of Fertility

Fertility studies in rats at doses of 5, 20, and 50 mg/kg/day of mefloquine have demonstrated adverse effects on fertility in the male at the high dose of 50 mg/kg/day, and in the female at doses of 20 and 50 mg/kg/day. Histopathological lesions were noted in the epididymides from male rats at doses of 20 and 50 mg/kg/day. Administration of 250 mg/week of mefloquine (base) in adult males for 22 weeks failed to reveal any deleterious effects on human spermatozoa.

Pregnancy

Teratogenic Effects

Pregnancy Category C. Mefloquine has been demonstrated to be teratogenic in rats and mice at a dose of 100 mg/kg/day. In rabbits, a high dose of 160 mg/kg/day was embryotoxic and teratogenic, and a dose of 80 mg/kg/day was teratogenic but not embryotoxic. There are no adequate and well-controlled studies in pregnant women. However, clinical experience with Lariam has not revealed an embryotoxic or teratogenic effect. Mefloquine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant. Women of childbearing potential should also be advised to practice contraception during malaria prophylaxis with Lariam and for up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination.

Nursing Mothers

Mefloquine is excreted in human milk in small amounts, the activity of which is unknown. Based on a study in a few subjects, low concentrations (3% to 4%) of mefloquine were excreted in human milk following a dose equivalent to 250 mg of the free base. Because of the potential for serious adverse reactions in nursing infants from mefloquine, a decision should be made

whether to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Use of Lariam to treat acute, uncomplicated *P. falciparum* malaria in pediatric patients is supported by evidence from adequate and well-controlled studies of Lariam in adults with additional data from published open-label and comparative trials using Lariam to treat malaria caused by *P. falciparum* in patients younger than 16 years of age. The safety and effectiveness of Lariam for the treatment of malaria in pediatric patients below the age of 6 months have not been established.

In several studies, the administration of Lariam for the treatment of malaria was associated with early vomiting in pediatric patients. 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 (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use

Clinical studies of Lariam did not include sufficient numbers of subjects aged 65 and over 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 Lariam (see **PRECAUTIONS**) 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.

ADVERSE REACTIONS

Clinical

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 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.

Postmarketing

Postmarketing surveillance indicates that the same kind of adverse experiences are reported during prophylaxis, as well as acute treatment.

The most frequently reported adverse events are nausea, vomiting, loose stools or diarrhea, abdominal pain, dizziness or vertigo, loss of balance, and neuropsychiatric events such as headache, somnolence, and sleep disorders (insomnia, abnormal dreams). These are usually mild and may decrease despite continued use.

Occasionally, more severe neuropsychiatric disorders have been reported such as: sensory and motor neuropathies (including paresthesia, tremor and ataxia), convulsions, agitation or restlessness, anxiety, depression, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, psychotic or paranoid reactions and encephalopathy. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed.

Other infrequent adverse events include:

Cardiovascular Disorders: circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular pulse, extrasystoles, A-V block, and other transient cardiac conduction alterations

Skin Disorders: rash, exanthema, erythema, urticaria, pruritus, edema, hair loss, erythema multiforme, and Stevens-Johnson syndrome

Musculoskeletal Disorders: muscle weakness, muscle cramps, myalgia, and arthralgia

Other Symptoms: visual disturbances, vestibular disorders including tinnitus and hearing impairment, dyspnea, asthenia, malaise, fatigue, fever, sweating, chills, dyspepsia and loss of appetite

Laboratory

The most frequently observed laboratory alterations which could be possibly attributable to drug administration were decreased hematocrit, transient elevation of transaminases, leukopenia and thrombocytopenia. These

alterations were observed in patients with acute malaria who received treatment doses of the drug and were attributed to the disease itself.

During prophylactic administration of mefloquine to indigenous populations in malaria-endemic areas, the following occasional alterations in laboratory values were observed: transient elevation of transaminases, leukocytosis or thrombocytopenia.

Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist up to several weeks after the last dose.

OVERDOSAGE

In cases of overdosage with Lariam, the symptoms mentioned under **ADVERSE REACTIONS** may be more pronounced. The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances.

DOSAGE AND ADMINISTRATION (see INDICATIONS AND USAGE)

Adult Patients

Treatment of mild to moderate malaria in adults caused by P. vivax or mefloquine-susceptible strains of P. falciparum

Five tablets (1250 mg) mefloquine hydrochloride to be given as a single oral dose. The drug should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

If a full-treatment course with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

> *Note:* 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 derivative (eg, primaquine).

Malaria Prophylaxis

One 250 mg Lariam tablet once weekly.

Prophylactic drug administration should begin 1 week before arrival in an endemic area. Subsequent weekly doses should be taken regularly, always on the same day of each week, preferably after the main meal. To reduce the risk of malaria after leaving an endemic area, prophylaxis must be continued for 4

additional weeks to ensure suppressive blood levels of the drug when merozoites emerge from the liver. Tablets should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

In certain cases, eg, when a traveler is taking other medication, it may be desirable to start prophylaxis 2 to 3 weeks prior to departure, in order to ensure that the combination of drugs is well tolerated (see **PRECAUTIONS: Drug Interactions**).

When prophylaxis with Lariam fails, physicians should carefully evaluate which antimalarial to use for therapy.

Pediatric Patients

Treatment of mild to moderate malaria in pediatric patients caused by mefloquine-susceptible strains of P. falciparum

Twenty (20) to 25 mg/kg body weight. Splitting the total therapeutic dose into 2 doses taken 6 to 8 hours apart may reduce the occurrence or severity of adverse effects. Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. 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.

If a full-treatment course with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

In pediatric patients, the administration of Lariam for the treatment of malaria has been associated with early vomiting. In some cases, early vomiting has been cited as a possible cause of treatment failure (see **PRECAUTIONS**). If a significant loss of drug product is observed or suspected because of vomiting, a second full dose of Lariam should be administered to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30 to 60 minutes after a dose, an additional half-dose should be given. If vomiting recurs, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time.

The safety and effectiveness of Lariam to treat malaria in pediatric patients below the age of 6 months have not been established.

Malaria Prophylaxis

The following doses have been extrapolated from the recommended adult dose. Neither the pharmacokinetics, nor the clinical efficacy of these doses have been determined in children owing to the difficulty of acquiring this

information in pediatric subjects. The recommended prophylactic dose of Lariam is approximately 5 mg/kg body weight once weekly. One 250 mg Lariam tablet should be taken once weekly in pediatric patients weighing over 45 kg. In pediatric patients weighing less than 45 kg, the weekly dose decreases in proportion to body weight:

30 to 45 kg:	¾ tablet
20 to 30 kg:	½ tablet
10 to 20 kg:	¼ tablet
5 to 10 kg:	tablet*

*Approximate tablet fraction based on a dosage of 5 mg/kg body weight. Exact doses for children weighing less than 10 kg may best be prepared and dispensed by pharmacists.

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

HOW SUPPLIED

Lariam is available as scored, white, round tablets, containing 250 mg of mefloquine hydrochloride in unit-dose packages of 25 (NDC 0004-0172-02). Imprint on tablets: LARIAM 250 ROCHE

Tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

ANIMAL TOXICOLOGY

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.

LARIAM® (mefloquine hydrochloride)

R_X only

Manufactured by:

F. HOFFMANN-LA ROCHE LTD

Basel, Switzerland

Distributed by:

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

XXXXXXXX-XXXX

Revised: December 2002

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019591/S-014&017

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 19-591

REVIEWER : Shukal Bala
CORRESPONDENCE DATE : 11-06-2000
CDER RECEIPT DATE : 11-08-2000
REVIEW ASSIGN DATE : 02-23-2001
REVIEW COMPLETE DATE : 05-04-2001

SPONSOR: Hoffmann-La-Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

SUBMISSION REVIEWED: SLR-017

DRUG CATEGORY: Anti-parasitic

INDICATION: (b) (4)

DOSAGE FORM: Tablets for oral administration

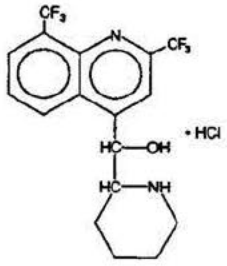
PRODUCT NAMES:

a. **PROPRIETARY:** Lariam®

b. **NONPROPRIETARY:** Mefloquine hydrochloride

c. **CHEMICAL:** (R*,S*)-±-α-2-piperidinyl-2,8-bis (trifluoromethyl)-4-quinolinemethanol hydrochloride

STRUCTURAL FORMULA:



Molecular weight: 414.78
Empirical formula: (b) (4)

SUPPORTING DOCUMENTS: None

BACKGROUND:

The subject of this NDA supplement is Lariam approved for the (b) (4)
(b) (4)
In this submission the sponsor has proposed changes in the Microbiology section of the label.

The LABEL (changes proposed by the sponsor):

The sponsor has proposed to modify and reformat the information as described below. The

(b) (4)

This information is followed by pk information.

Pages 3 - 4

~~**Microbiology:** Strains of Plasmodium falciparum resistant to mefloquine have been reported.~~

(b) (4)

References:
1. Hopperus Buma *et al*., 1996. J Inf Dis 173: 1506.
2. Brasseur *et al*., 1992. Am J Trop Med Hyg 46: 8.

Comments:

- The sponsor has proposed to change the Microbiology section of the label. However, it is of note that the changes proposed are not consistent in terms of content or format with current practice.

- The following statements in the mechanism of action section of the proposed label are not supported by any studies

(b) (4)

At the present time mefloquine is approved for *P. falciparum* and *P. vivax*. The current approved label also states that
mefloquine in malaria caused by *P. ovale* and *P. malariae*." (b) (4)

(b) (4)

(b) (4)

-

Hopperus Buma *et al*., 1996 (J Inf Dis 173: 1506) shows the prevalence of mefloquine resistance in South East Asia. This study is based on 2289 Dutch marines (sent as 3 battalions at different times) serving in different parts of Western Cambodia. Prophylaxis was initiated with mefloquine (250 mg/week) 1 to 2 weeks prior to departure to Cambodia and continued for until 4 weeks after return from the endemic area. A total of 64 cases of malaria were diagnosed in 59 marines. Of these, 42 cases were with *P. falciparum* infection and 22 with *P. vivax*. Of the *P. falciparum* infections, 31 occurred in Cambodia and 11 upon return from the endemic area. All *P. vivax* infections occurred upon return from Cambodia.

It appears that blood from subjects with parasitemia was cultured and processed for measurement of *in vitro* susceptibility to mefloquine. However, the details of the experimental design and results were not included in the report. It was stated that "falciparum parasites isolated from 4 Dutch patients were resistant *in vitro* to mefloquine."

Based on the study described above and other reports available in the literature it would be a useful information for a traveler visiting Southeast Asia where malaria parasites are known to be resistant to mefloquine. (b) (4) Therefore, it will be worthwhile to state that incidences of increased resistance to mefloquine have been reported in other parts of the world.

- The sponsor has proposed to state that "cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed in some regions." In a study by Brasseur *et al.*, 1992 (Am J Trop Med Hyg 46: 8), the development of cross-resistance between mefloquine and quinine in some regions of Cameroon was shown. The results in Figure 1 show that about 20% (26/133) of the isolates from the North region of Cameroon were resistant to mefloquine using a relative cut-off of 30 nM (IC_{50} of >30 nM). A majority of the isolates from southwestern region were susceptible to mefloquine *in vitro*. In addition, 19/133 isolates were intermediate in susceptibility to mefloquine (IC_{50} between 20-30 nM). It is of note that these studies were done at a time when mefloquine was not administered in the area. However, the population in the Northern region was considered to be under high quinine drug pressure.

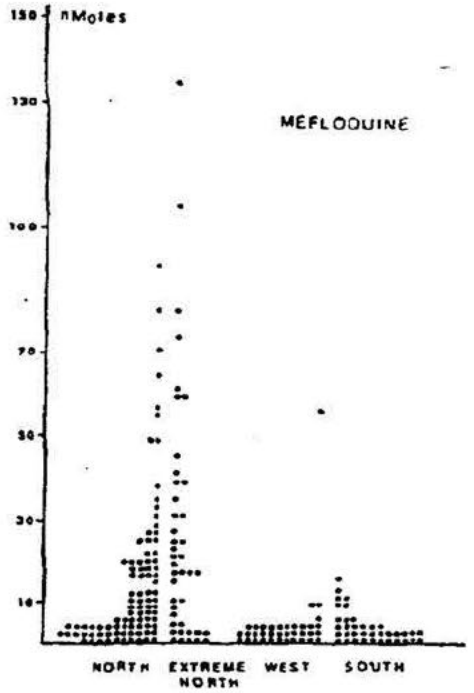


FIGURE 1. Sensitivity to mefloquine in 206 isolates studied in vitro. Concentrations effective at 50% (EC_{50} are expressed in nanomoles/liter.

Attempts were made to measure resistance *in vivo*. For this, 46 patients were administered a single dose of mefloquine (25 mg/kg) and parasitemia followed for 8 days. Parasitemia was cleared within 7 days in 40 patients. The remaining 6 patients were considered to exhibit RII-RIII level of mefloquine resistance. *In vitro* susceptibility of isolates, from 42/46 subjects including the 4 patients with RII-III resistance *in vivo*, was measured by incorporation of ^{3}H-hypoxanthine. The results in Figure 2 show the IC_{50} values to mefloquine, chloroquine and quinine. No cross-resistance between mefloquine and chloroquine was observed. However, a positive correlation between mefloquine and quinine IC_{50} values for the isolates from the northern region indicate cross-resistance between the 2 drugs. In the Southwestern region there was no correlation between mefloquine and quinine susceptibility. There was a co-existence of resistance to chloroquine and quinine.

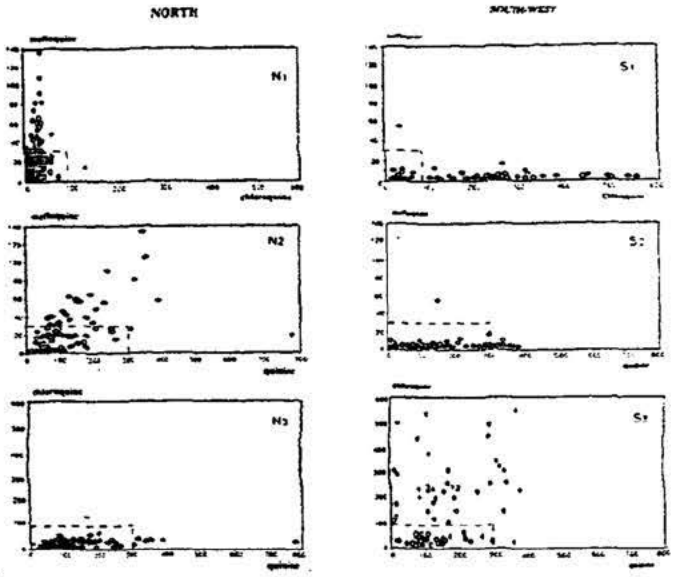


Figure 2 Comparison of the responses to chloroquine, quinine, and mefloquine in isolates studied in the dry northern area (N) and the wet southwestern area (S) of Cameroon.

Cross-resistance with halofantrine was not reported in this study. However, there are reports available in the literature (e.g., Schlagenhauf, P., 1999, J Travel Med 6: 122) demonstrating cross-resistance between mefloquine and halofantrine.

CONCLUSIONS:

The sponsor has proposed to change the Microbiology section of the label. However, it is of note that the Microbiology section of the label is not consistent in terms of content or format with current practice. In addition some of the statements proposed by the sponsor to be included in the label are not supported by studies. Based on the information available at the present time and the comments discussed above the changes proposed to the label are as follows:

The Label (changes recommended):

It is recommended that the text be organized under a subheading of Microbiology and divided into 4 sections (i.e., Mechanism of Action, Activity *in vitro* and *in vivo,* Drug resistance, and Cross resistance) in the Clinical Pharmacology section as shown below:

CLINICAL PHARMACOLGY:

(b) (4)

exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see INDICATIONS and USAGE).

Drug Resistance (b) (4) Strains of *P. falciparum* with decreased susceptibility to mefloquine can be selected *in vitro* or *in vivo*. Resistance of *P. falciparum* to mefloquine has been reported, ~~predominantly~~ in areas of multi-drug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

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

e

(b) (4)

Shukal Bala
Microbiologist, HFD-590

CONCURRENCES:
HFD-590/Deputy Dir. _____Signature _____Date
HFD-590/MicroTL _____Signature _____Date
CC:
HFD-590/Original NDA # 19-591
HFD-590/Division File
HFD-590/MO
HFD-590/Pharm
HFD-590/Chem
HFD-590/Review Micro
HFD-590/CSO/JensenV

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shukal Bala
5/9/01 05:10:46 PM
MICROBIOLOGIST

Kenneth Hastings
5/10/01 08:28:01 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-014&017

CLINICAL PHARMACOLOGY REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	19-591
Serial No:	SLR-014, SLR-017
Generic	Mefloquine Hydrochloride
(Brand®)	Lariam
Submission Date:	August 19, 1999, November 6, 2000
Sponsor:	Hoffmann-La Roche Inc.
Type of Submission:	Labeling Supplement
Reviewer:	Houda Mahayni

Submission

SLR-014

The sponsor is submitting a labeling supplement that contains package insert revisions consistent with the worldwide safety information that is available on this product. The sponsor is submitting SLR-014 supplement for the purpose of abiding with a final rule published in the Federal Register notice dated August 27, 1997. This final rule establishes a "Geriatric Use" subsection under the PRECAUTIONS section of the package insert that provides information on the safe and effective use of drugs in elderly patients aged 65 and older.

To include all the relevant information necessary in this subsection the sponsor performed the following:

- A literature search based on the ROSCOPES database (dated April 6, 1999) covering the life of the product through April 6, 1999.
- Hoffmann-La Roche Inc. safety information which provided a breakdown of Lariam adverse events reported worldwide in patients 65 years and older compared with events reported in patients aged less than 65 years (cummulative over the life of the product through March 31, 1999).

As no new pharmacokinetic data were identified regarding the use of Lariam in geriatric patients, the new subsection will now contain the following wording:

Geriatric Use: Clinical studies of Lariam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. (b) (4)

(b) (4)

(b) (4) The benefits of Lariam therapy should be weighed against the possibility of adverse effects in patients with cardiac disease (see PRECAUTIONS).

SLR-017

In this submission, the sponsor is providing a revised package insert to reflect the change in dosage strength and appearance of the tablet (Global Harmonization, see SCF-016 submission). Also, the package insert has been revised to reflect consistency with the worldwide safety information that is available on the product.

Reviewer's Comments

Clinical Pharmacology **(Text that should be deleted is strikethrough, text that should be added contains a double underline).**

Absorption section should read as follows:

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. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, 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). In healthy volunteers, ~~at~~ a dose of 250 mg once weekly produces maximum steady state plasma concentrations of 1000 to 2000 µg/L which are reached after 7 to 10 weeks.

Distribution section should read as follows:
In healthy adults, the apparent volume of distribution is approximately 20L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constan (b) (4) erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 min, was found to be reversible. Protein binding is about 98%. (b) (4)

(b) (4)

Elimination section should read as follows:
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 under steady-state condition accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine.

Pharmacokinetics In Special Clinical Situtations section:

(b) (4)

Although clearance of mefloquine may increase in late pregrancy, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

(b) (4)

During long-term prophylaxis (≥ 2 years), the trough concentrations and the elimination half-life of mefloquine were similar to those obtained in the same population after 6 months of drug use. (b) (4)

DOSAGE AND ADMINISTRATION section:

(b) (4)

The drug should not be taken on an empty stomach and should be administered with ample water. For very young patients, the dose may be crushed, mixed with water or sugar water and may be administered via an oral syringe.

Recommendations
For supplements (SLR-014 and SLR-017), please ask the sponsor to adopt the above modifications to the package insert.

Comments (to be sent to firm)
Please pass the modified version of the label to the sponsor.

Houda Mahayni, R.Ph., Ph.D.

Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

FT/RD initialed by Funmi Ajayi, Ph.D., Team Leader

/s/

Houda Mahayni
4/11/01 11:21:42 AM
BIOPHARMACEUTICS

Funmilayo Ajayif
4/16/01 03:05:55 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-014&017

OTHER REVIEW(S)

Labeling, Clinical, Biopharmaceutics and Microbiology Review of Supplemental Labeling Revisions (SLRs):

Sponsor: Hoffman LaRoche, Inc.

Product: Lariam® (mefloquine hydrochloride) Tablets, 250 mg

Materials Reviewed:

SLR	Date submitted	Date received	Date completed
014	August 19, 1999	August 24, 1999	January 3, 2003
017	November 6, 2000	November 8, 2000	January 3, 2003
Amendments			
014, 017	December 2, 2002	December 6, 2002	January 3, 2003
014, 017	December 19, 2002	December 23, 2002	January 3, 2003

- Approved package insert for NDA 19-591 dated October 3, 2002
- Dr. Houda Mahayni's biopharmaceutics review of S-014 and S-017 dated April 16, 2001
- Dr. Shukal Bala's microbiology review of S-017 dated May 9, 2001
- FDA fax to Hoffman LaRoche with proposed labeling revisions dated October 31, 2002

Background:
NDA 19-591 (Tablets) was originally approved on May 2, 1989. The last labeling change for the Lariam® package insert occurred on October 3, 2002, when a changes being effected (CBE) labeling supplement adding psychiatric symptoms was approved. No other labeling changes have been approved since that time.

Supplement 014 was submitted for prior approval and provides for the addition of a new **Geriatric Use** subsection in the **PRECAUTIONS** section of the package insert. In her review of this supplement dated April 16, 2001, Dr. Houda Mahayni, Biopharmaceutics Reviewer did not recommend any changes to the sponsor's proposed **Geriatric Use** statement. During an internal team meeting on October 1, 2002 and in an e-mail message on that same day, Dr. Leonard Sacks, Medical Officer stated that (b) (4) (b) (4) He recommended that the **Geriatric Use** statement be revised a s follows:

Double underline=FDA added text to company's proposed text
~~Strikethrough~~=FDA deleted text to company's proposed text

> Clinical Studies of Lariam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between elderly and younger patients. Since electrocardiographic abnormalities have been observed in individuals treated with Lariam (see **PRECAUTIONS**) and underlying cardiac disease is more prevalent in elderly than in younger patients, (b) (4) the benefits of Lariam therapy should be weighed against the possibility of adverse cardiac effects in elderly patients (b) (4) (b) (4)

Supplement 017 was submitted for prior approval and provides for multiple changes to the package insert to reflect the change in dosage strength and appearance of the tablet (Global Harmonization, see SCF-016 submission). Also, the package insert was revised to reflect consistency with the worldwide safety information that is available concerning the product.

In her review of this supplement dated April 16, 2001, Dr. Mahayni recommended the following changes to the company's proposed wording:

Double underline=FDA added text to company's proposed text
~~Strikethrough~~=FDA deleted text to company's proposed text
*Italic*s=reviewer comment

CLINICAL PHARMACOLOGY
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. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, 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). In healthy volunteers, ~~at~~ a dose of 250 mg once weekly produces maximum steady state plasma concentrations of 1000 to 2000 µg/L which are reached after 7 to 10 weeks.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constant ~~at an~~ erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 min, was found to be reversible. Protein binding is about 98%. (b) (4) (b) (4)

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 under steady-

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(b) (4)

DOSAGE AND ADMINISTRATION

(b) (4)

(b) (4)

The drug should not be taken on an empty stomach and should be administered

(b) (4) (b) (4)

(b) (4)

In an e-mail message dated October 3, 2002, Dr. Dakshina Chilukuri, Biopharmaceutics Reviewer stated that most of the comments proposed by Dr. Mayhayni last year for S-017 were still relevant, however her comment for the **DOSAGE AND ADMINISTRATION** section should not be communicated to the company since the current Biopharmaceutic reviewers found the company's proposed wording to be acceptable.

Dr. Shukal Bala, Microbiology Team Leader reviewed the Microbiology changes proposed in S-017. In her review dated May 9, 2001 she made following comments:

The text should be organized under a subheading of Microbiology and divided into 4 sections (i.e., Mechanism of Action, Activity in vitro and in vivo, Drug resistance, and Cross resistance) in the Clinical Pharmacology section as shown below:

CLINICAL PHARMACOLOGY

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effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see INDICATIONS and USAGE).

Drug Resistance (b) (4) Strains of *P. falciparum* with decreased susceptibility to mefloquine can be selected *in vitro* or *in vivo*. Resistance of *P. falciparum* to mefloquine has been reported, (b) (4) in areas of multi-drug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

(b) (4)

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FDA labeling revisions and the supporting data for the microbiology changes requested in the October 31, 2002 fax was received by the Division on December 6, 2002.

Also, following the initial label comparison of the December 2, 2002 proposed label and the October 3, 2002 approved label it was noted that several changes had been made to the **DOSAGE AND ADMINISTRATION** section of the package insert that had not been previously discussed with the Division. The company was called by the review team on December 17, 2002, and Ms. Lynn DeVenezia Tobias stated that these changes were connected to chemistry changes proposed in SCF-016. The company planned to withdraw SCF-016 and also would therefore withdraw the labeling changes proposed in **DOSAGE AND ADMINISTRATION** in S-017.

In an e-mail message dated December 18, 2002, Dr. Bala stated that the information in the review articles submitted in support of (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) That day Ms. DeVenezia Tobias was called and advised to submit a revised label with the following revisions made to the label originally proposed on December 2, 2002:

1. **Microbiology** subsection in **CLINICAL PHARMACOLOGY** should be revised to reflect Dr. Bala's comments noted above.

2. **DOSAGE AND ADMINISTRATION** section should revised to delete the proposed labeling changes associated with S-016.

The revised Lariam label was received by the Division on December 23, 2002.

Note: Dr. Bala later mentioned that *Plasmodium falciparum* should be written in full the first time it is mentioned in the micro section. Since the company had already prepared the revised label it was agreed that this would be mentioned a s a minor editorial correction and would be corrected when final printed labeling was submitted.

On January 6, 2003, Dr. Chilukuri noted that in the December 19, 2002 version of the label the agreed upon wording in the **Dosage and Administration, Pediatric Patients** subsection was inadvertently omitted. The last sentence in the first paragraph should be changed from:

(b) (4)

To

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.

Electronic Labeling Comparison:
The approved Lariam package insert dated October 3, 2002 was electronically compared to the proposed draft package insert dated December 20, 2002. The changes were as follows:

Added text=double underline
Deleted text=~~strikethrough~~

1. CLINICAL PHARMACOLOGY

•This entire section was revised. A **Pharmacokinetic** subsection was added with subheadings, and the **Microbiology** subsection was revised to read:

Pharmacokinetics

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formation 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. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, 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). In healthy volunteers, a dose of 250 mg once weekly, produces maximum steady-state plasma concentrations of 1000 to 2000 µg/L, which are reached after 7 to 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. Experiments conducted in vitro with human blood using concentrations between 50 and 1000 mg/mL showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes, was found to be reversible. Protein binding is about 98%.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see **PRECAUTIONS: Nursing Mothers**).

Metabolism

Two metabolites have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *P. falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2 to 4 hours after a single oral dose. Maximum plasma concentrations, 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 under steady-state condition accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine.

Pharmacokinetics in Special Clinical Situations

Children and the Elderly

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.

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. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy persons.

Although clearance of mefloquine may increase in late pregnancy, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

The pharmacokinetics of mefloquine may be altered in acute malaria.

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.

During long-term prophylaxis (>2 years), the trough concentrations and the elimination half-life of mefloquine were similar to those obtained in the same population after 6 months of drug use, which is when they reached steady state.

In vitro and in vivo studies showed no hemolysis associated with glucose-6-phosphate dehydrogenase deficiency (see **ANIMAL TOXICOLOGY**).

~~Pharmacokinetic studies of mefloquine in healthy male subjects showed that a significant lagtime occurred after drug administration, and the terminal elimination half-life varied widely (13 to 24 days) with a mean of about 3 weeks.~~

~~Mefloquine is a mixture of enantiomeric molecules whose rates of release, absorption, transport, action, degradation and elimination may differ. A valid pharmacokinetic model may not exist in such a case.~~
~~Additional studies in European subjects showed slightly greater concentrations of drug for longer periods of time. The absorption half-life was 0.36 to 2 hours, and the terminal elimination half-life was 15 to 33 days. The primary metabolite was identified and its concentrations were found to surpass the concentrations of mefloquine.~~
~~Multiple-dose kinetic studies confirmed the long elimination half-lives previously observed. The mean metabolite to mefloquine ratio measured at steady-state was found to range between 2.3 and 8.6.~~
~~The total clearance of the drug, which is essentially all hepatic, is approximately 30 mL/min. The volume of distribution, approximately 20 L/kg, indicates extensive distribution. The drug is highly bound (98%) to plasma proteins and concentrated in blood erythrocytes, the target cells in malaria, at a relatively constant erythrocyte-to-plasma concentration ratio of about 2.~~
~~The pharmacokinetics of mefloquine in patients with compromised renal function and compromised hepatic function have not been studied.~~

Microbiology

Mechanism of Action

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

~~***Microbiology:*** **Strains of Plasmodium falciparum resistant to mefloquine have been reported.**~~

Activity In Vitro and In Vivo

Mefloquine is active against the erythrocytic stages of *Plasmodium* species (see **INDICATIONS AND USAGE**). However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see **INDICATIONS AND USAGE**).

Drug Resistance

Strains of *P. falciparum* with decreased susceptibility to mefloquine can be selected in vitro or in vivo. Resistance of *P. falciparum* to mefloquine has been reported, in areas of multi-drug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

Cross Resistance

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

2. CONTRAINDICATIONS

The first sentence in this section was revised to read:

> Use of Lariam is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds (eg, quinine and quinidine) or to any of the excipients contained in the formulation.

3. PRECAUTIONS

- The **first two paragraphs in the General** subsection were revised to read;:

> **General**
>
> Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.
>
> ~~***General:***~~ In patients with epilepsy, Lariam may increase the risk of convulsions. The drug should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see **PRECAUTIONS: Drug Interactions**).
>
> Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving, piloting aircraft, operating machinery, and deep-sea diving, as dizziness, a loss of balance, or other disorders of the central or peripheral nervous system have been reported during and following the use of Lariam. These effects may occur after therapy is discontinued due to the long half-life of the drug. Lariam should be used with caution in patients with psychiatric disturbances because mefloquine use has been associated with emotional disturbances (see **ADVERSE REACTIONS**).

- The fourth bullet in the **Information for Patients** subsection was revised to read:

> - that when used as prophylaxis, the first dose of Lariam should be taken 1 week prior to ~~departure~~ arrival in an endemic area;

- The second paragraph in the **Drug Interactions** subsection was revised to read:

> Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine ~~should~~ must not be given simultaneously with or subsequent to Lariam (see **WARNINGS**).

- The seventh paragraph in the **Drug Interactions** subsection was revised to read:

> No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving comedication, particularly ~~those on coagulants or antidiabetics~~ diabetics or patients using anticoagulants, should be checked before departure.

•The following statements were added to the end of the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, **Pregnancy, Teratogenic Effects** statement:

> Women of childbearing potential should also be advised to practice contraception during malaria prophylaxis with Lariam and up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination.

•The following phrase was added to the first sentence in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, **Nursing Mothers** statement:

> Mefloquine is excreted in human milk in small amounts, the activity of which is unknown.

•A **Geriatric Use** subsection was added to the end of this section to read:

> Clinical studies of Lariam did not include sufficient numbers of subjects aged 65 and over 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 Lariam (see **PRECAUTIONS**) 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.

4. ADVERSE REACTIONS

•A reference was added to the first sentence in the fourth paragraph to read:

> 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.

5. OVERDOSAGE

•This section was revised to read:

> In cases of overdosage with Lariam, the symptoms mentioned under **ADVERSE REACTIONS** may be more pronounced. The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate. Monitor cardiac function (if possible by ECG) and neuro~~logic and~~ psychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances. ~~Treat vomiting or diarrhea with standard fluid therapy.~~

6. DOSAGE AND ADMINISTRATION (see INDICATIONS AND USAGE)

•The **Adult Patients** subsection was revised to read:

Treatment of mild to moderate malaria in adults caused by P. vivax or mefloquine-susceptible strains of P. falciparum

Five tablets (1250 mg) mefloquine hydrochloride to be given as a single oral dose. The drug should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

If a full-treatment course ~~has been administered without clinical cure, alternative treatment should be given~~ with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

Note: 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 derivative (eg, primaquine).

Malaria Prophylaxis

One 250 mg Lariam tablet once weekly.

Prophylactic drug administration should begin 1 week before ~~departure to~~ arrival in an endemic area. Subsequent weekly doses should ~~always~~ be taken regularly, always on the same day of ~~the~~ each week, preferably after the main meal. To reduce the risk of malaria after leaving an endemic area, prophylaxis ~~should~~ must be continued for 4 additional weeks to ensure suppressive blood levels of the drug when merozoites emerge from the liver. Tablets should not be taken on an empty stomach and should be administered with at least 8 oz (240 mL) of water.

In certain cases, eg, when a traveler is taking other medication, it may be desirable to start prophylaxis 2 to 3 weeks prior to departure, in order to ensure that the combination of drugs is well tolerated (see **PRECAUTIONS: Drug Interactions**).

When prophylaxis with Lariam fails, physicians should carefully evaluate which antimalarial to use for therapy.

•The **Pediatric Patients** subsection was revised to read:

Treatment of mild to moderate malaria in pediatric patients caused by mefloquine-susceptible strains of P. falciparum

Twenty (20) to 25 mg/kg ~~for non-immune patients~~ body weight. Splitting the total ~~curative~~ therapeutic dose into 2 doses taken 6 to 8 hours apart may reduce the

occurrence or severity of adverse effects. Experience with Lariam in infants less than 3 months old or weighing less than 5 kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water.

~~For very young patients, the dose may be crushed, mixed with water or sugar water and may be administered via an oral syringe.~~ 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.

If a full-treatment course ~~has been administered without clinical cure, alternative treatment should be given~~ with Lariam does not lead to improvement within 48 to 72 hours, Lariam should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, Lariam should not be used for curative treatment.

In pediatric patients, the administration of Lariam for the treatment of malaria has been associated with early vomiting. In some cases, early vomiting has been cited as a possible cause of treatment failure (see **PRECAUTIONS**). If a significant loss of drug product is observed or suspected because of vomiting, a second full dose of Lariam should be administered to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30 to 60 minutes after a dose, an additional half-dose should be given. If vomiting recurs, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time.

The safety and effectiveness of Lariam to treat malaria in pediatric patients below the age of 6 months have not been established.

Malaria Prophylaxis

The following doses have been extrapolated from the recommended adult dose. Neither the pharmacokinetics, nor the clinical efficacy of these doses have been determined in children owing to the difficulty of acquiring this information in pediatric subjects. The recommended prophylactic dose of Lariam is ~~3 to~~ approximately 5 mg/kg body weight once weekly. One 250 mg Lariam tablet should be taken once weekly in pediatric patients weighing over 45 kg. In pediatric patients weighing less than 45 kg, the weekly dose decreases in proportion to body weight:

30 to 45 kg:	¾ tablet
20 to 30 kg:	½ tablet
~~up~~ 10 to 20 kg:	¼ tablet
5 to 10 kg:	⅛ tablet*

*Approximate tablet fraction based on a dosage of 5 mg/kg body weight. Exact doses for children weighing less than 10 kg may best be prepared and dispensed by pharmacists.

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

7. **HOW SUPPLIED**

The last sentence in this section was revised to read:

> Tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Conclusions/Recommendations:
These labeling changes are acceptable. An approval letter should be sent advising the applicant that these supplemental NDA submissions are approved with the two minor editorial corrections noted by Dr. Bala and Dr. Chilukuri.

Robin Anderson, R.N., M.B.A.
Labeling Reviewer

Leonard Sacks, M.D.
Medical Officer

Dakshina Chilukuri, Ph. D.
Biopharmaceutics Reviewer

Shukal Bala, Ph. D
Microbiology Team Leader

cc:
HFD-590/MO/L. Sacks
HFD-590/MedTL/R. Roca
HFD-590/S. Bala/MicroTL
HFD-590/Biopharm/D. Chilukuri
HFD-590/BiopharmTL/B. Davit
HFD-590/DivDir/R. Albrecht
HFD-590/PM/J. Saliba

Concurrence:
HFD-590/MO/L. Sacks 1/7/03
HFD-590/MedTL/R. Roca 1/7/03
HFD-590/S. Bala/MicroTL 1/6/03
HFD-590/Biopharm/D. Chilukuri1/6/03
HFD-590/BiopharmTL/B. Davit 1/6/03
HFD-590/DivDir/R. Albrecht 1/7/03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robin Anderson
1/8/03 10:59:01 AM
INTERDISCIPLINARY

Renata Albrecht concurred with this review on 1/7/03.

Renata Albrecht
1/10/03 02:16:30 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-014&017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-591/S-015
NDA 19-591/S-016
NDA 19-591/S-017

PRIOR APPROVAL SUPPLEMENT

Hoffman-La Roche Inc.
Attention: Ms. Duane L. Voss,
Program Director
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Voss:

Please refer to your supplemental new drug application submitted November 6, 2000 and received November 8, 2000 for Lariam® (mefloquine hydrochloride) Tablets 250 mg. Refer also to our a

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(b) (4)

We have administratively created a separate supplement for all of the remaining proposed changes. For your records, please note that we have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lariam® (mefloquine hydrochloride) Tablets, 250 mg

NDA Number: 19-591

Supplement Number: S-017

Date of Supplement: November 6, 2000

Date of Receipt: November 8, 2000

This supplement proposes the following change(s):

- Revisions to the **CLINICAL PHARMACOLOGY** section of the label.
- Revisions to the **PRECAUTIONS, *Drug Interactions*** subsection of the label.
- Revisions to the **PRECAUTIONS, *Geriatric Use*** subsection of the label.
- Revisions to the **ADVERSE REACTIONS, *Clinical*** subsection of the label.
- Revisions to the **DOSAGE AND ADMINISTRATION** section of the label.

Please cite the application numbers listed above at the top of the first page of any communications concerning these supplemental applications. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Valerie Jensen, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Ellen Frank
3/2/01 01:47:59 PM
NDA 19-591/S-015, NDA 19-591/S-016, 19-591/S-017