CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 019591/S-023

Trade Name:	Lariam for oral use, 250mg
Generic or Proper Name:	Mefloquine Hydrochloride
Sponsor:	Hoffman-LaRoche, Inc.
Approval Date:	May 12, 2008
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*.

CENTER FOR DRUG EVALUATION AND RESEARCH
NDA 019591/S-023
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-023

Hoffmann-La Roche, Inc.
Attention: Ms. Lynn DeVenezia-Tobias
Program Manager
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug application dated November 9, 2007, received November 13, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

This supplemental new drug application provides for addition of new information to the **ADVERSE REACTIONS/Postmarketing** subsection and the **OVERDOSAGE** section of the Lariam labeling to include information on pneumonitis, of possible allergic etiology, which was observed in post-market data.

The following revisions (~~strikethrough~~ = deleted and underlined = added) to the text for the package insert for Lariam were proposed in this supplemental application:

1. The following was added alphabetically under "Other infrequent adverse events include:" in the **ADVERSE REACTIONS/Postmarketing** subsection:

   Respiratory Disorders: dyspnea, pneumonitis of possible allergic etiology

2. The **OVERDOSAGE** section was modified as follows:

   Symptoms and Signs

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

   Treatment

   ~~The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate.~~ Patients should be managed by symptomatic and supportive care following Lariam overdose. There are no specific antidotes. 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.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**SPL for approved supplement NDA 19-591/S-023**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Kristen Miller, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

5/12/2008 06:01:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-023

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-023 **PRIOR APPROVAL SUPPLEMENT**

Hoffmann-La Roche Inc.
Attention: Ms. Lynn DeVenezia-Tobias
Program Manager
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. DeVenezia-Tobias:

We have received your supplemental new 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: 023

Date of supplement: November 9, 2007

Date of receipt: November 13, 2007

This supplemental application proposes the following revisions to the product label (underline indicates addition; ~~strikethrough~~ indicates deletion):

- Under **ADVERSE REACTIONS/Postmarketing**,

  Respiratory Disorders: dyspnea, pneumonitis of possible allergic etiology

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

- Under **OVERDOSAGE**,

  Symptoms and Signs

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

Treatment

~~The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate.~~ (b) (4) 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.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 11, 2007 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Special Pathogen and Transplant Drug Products
Office of Antimicrobial Drug Products
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/

Diana Willard
11/28/2007 02:47:28 PM
NDA 19-591/S-023 Acknowledgement

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-023

LABELING

LARIAM®

brand of

mefloquine hydrochloride

TABLETS

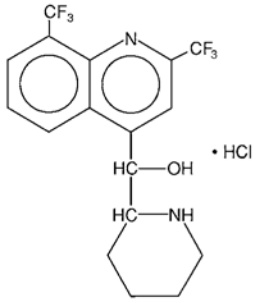
R_X only

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 *Plasmodium 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**).

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 *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.

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 derivative (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.

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

Medication Guide: As required by law, a Lariam Medication Guide is supplied to patients when Lariam is dispensed. An information wallet card is also supplied to patients when Lariam is dispensed. Patients should be instructed to read the Medication Guide when Lariam is received and to carry the information wallet card with them when they are taking Lariam. The complete texts of the Medication Guide and information wallet card are reprinted at the end of this document.

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.

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

Respiratory Disorders: dyspnea, pneumonitis of possible allergic etiology

Other Symptoms: visual disturbances, vestibular disorders including tinnitus and hearing impairment, 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

Symptoms and Signs

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

Treatment

Patients should be managed by symptomatic and supportive care following Lariam overdose. There are no specific antidotes. 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:	3/4 tablet
20 to 30 kg:	1/2 tablet
10 to 20 kg:	1/4 tablet
5 to 10 kg:	1/8 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)

Revised: Month Year

MEDICATION GUIDE

This Medication Guide is intended only for travelers who are taking Lariam to prevent malaria. The information may not apply to patients who are sick with malaria and who are taking Lariam to treat malaria.

An information wallet card is provided with this Medication Guide. Carry it with you when you are taking Lariam.

This Medication Guide was revised in May 2004. Please read it before you start taking Lariam and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your prescriber (doctor or other health care provider) about Lariam and malaria prevention. Only you and your prescriber can decide if Lariam is right for you. If you cannot take Lariam, you may be able to take a different medicine to prevent malaria.

What is the most important information I should know about Lariam?

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

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

3. **You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area.**
   Medicines approved in the United States for malaria prevention include Lariam, doxycycline, atovaquone/proguanil, hydroxychloroquine, and chloroquine. Not all of these drugs work equally as well in all areas of the

world where there is malaria. The chloroquines, for example, do not work in areas where the malaria parasite has developed resistance to chloroquine. Lariam may be effective against malaria that is resistant to chloroquine or other drugs. All drugs to treat malaria have side effects that are different for each one. For example, some may make your skin more sensitive to sunlight (Lariam does not do this). However, if you use Lariam to prevent malaria and you develop a sudden onset of anxiety, depression, restlessness, confusion (possible signs of more serious mental problems), or you develop other serious side effects, contact a doctor or other health care provider. It may be necessary to stop taking Lariam and use another malaria prevention medicine instead. If you can't get another medicine, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.

Who should not take Lariam?

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

- **have depression or had depression recently**
- **have had recent mental illness or problems,** including anxiety disorder, schizophrenia (a severe type of mental illness), or psychosis (losing touch with reality)
- **have or had seizures (epilepsy or convulsions)**
- **are allergic to quinine or quinidine (medicines related to Lariam)**

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

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

Tell your prescriber about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may give you a higher chance of having serious side effects from Lariam.

How should I take Lariam?

Take Lariam exactly as prescribed. If you are an adult or pediatric patient weighing 45 kg (99 pounds) or less, your prescriber will tell you the correct dose based on your weight.

To prevent malaria

- For adults and pediatric patients weighing over 45 kg, take 1 tablet of Lariam at least 1 week before you travel to a malaria area (or 2 to 3 weeks before you travel to a malaria area, if instructed by your prescriber). This starts the prevention and also helps you see how Lariam affects you and the other medicines you take. **Take 1 Lariam tablet once a week**, on the same day each week, while in a malaria area.

- **Continue taking Lariam for 4 weeks after returning from a malaria area.** If you cannot continue taking Lariam due to side effects or for other reasons, contact your prescriber.

- Take Lariam just after a meal and with at least 1 cup (8 ounces) of water.

- For children, Lariam can be given with water or crushed and mixed with water or sugar water. The prescriber will tell you the correct dose for children based on the child's weight.

- If you are told by a doctor or other health care provider to stop taking Lariam due to side effects or for other reasons, it will be necessary to take another malaria medicine. You must take **malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area. If you don't have access to a doctor or other health care provider or to another medicine besides Lariam and have to stop taking it, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.**

What should I avoid while taking Lariam?

- **Halofantrine (marketed under various brand names)**, a medicine used to treat malaria. Taking both of these medicines together can cause serious heart problems that can cause death.

- **Do not become pregnant.** Women should use effective birth control while taking Lariam.

- **Quinine, quinidine, or chloroquine (other medicines used to treat malaria).** Taking these medicines with Lariam could cause changes in your heart rate or increase the risk of seizures.

In addition:

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

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

What are the possible side effects of Lariam?

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

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

Lariam may affect your liver and your eyes if you take it for a long time. Your prescriber will tell you if you should have your eyes and liver checked while taking Lariam.

What else should I know about preventing malaria?

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

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

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

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

- **Protect against mosquito bites**. Medicines do not always completely prevent your catching malaria from mosquito bites. So protect yourself very well against mosquitoes. Cover your skin with long sleeves and long pants, and use mosquito repellent and bednets while in malaria areas. If you are out in the bush, you may want to pre-wash your clothes with permethrin. This is a mosquito repellent that may be effective for weeks after use. Ask your prescriber for other ways to protect yourself.

General information about the safe and effective use of Lariam.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide Revised: May 2004

Reprint of information wallet card:

679

Lariam® (mefloquine hydrochloride) **Tablets**

Carry this information wallet card with you when you are taking Lariam.

You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area.

If taken correctly, Lariam is effective at preventing malaria but, like all medications, it may produce side effects in some patients.

If you use Lariam to prevent malaria and you develop a sudden onset of anxiety, depression, restlessness, confusion (possible signs of more serious mental problems), or you develop other serious side effects, contact a doctor or other health care provider. It may be necessary to stop taking Lariam and use another malaria prevention medicine instead.

Other medicines approved in the United States for malaria prevention include: doxycycline, atovaquone/proguanil, hydroxychloroquine, and chloroquine. Not all malaria medicines work equally well in malaria areas. The chloroquines, for example, do not work in many parts of the world. If you can't get another medicine, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.

Please read the Medication Guide for additional information on Lariam.

Card Revised: May 2004

680

681

682 Manufactured by:
683 F. HOFFMANN-LA ROCHE LTD
684 Basel, Switzerland

685 Distributed by:

Pharmaceuticals

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

687 xxxxxxxx

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019591/S-023

CLINICAL REVIEW(S)

NDA 19-591, S-023
Medical Officer Review of Lariam® Prescriber Information and Lariam® Medication Guide Pertaining to Pneumonitis

Review Completed: Dec 31st, 2007

Medical Officer: Elizabeth O'Shaughnessy, M.D.

Acting Team Leader: Joette Meyer, Pharm. D.

Division Director: Renata Albrecht, M.D.

Project Manager: Kristen Miller, Pharm. D.

Sponsor: F. Hoffmann-La Roche LTD
Roche Pharmaceuticals

Drug Name: Lariam®

Generic Name: Mefloquine hydrochloride

Drug Formulation: Tablet

Dosing Regimen: Prophylaxis: 250mg once weekly
Treatment: 1250mg single dose

Indication(s): (b) (4)

Material(s) Reviewed: Current Prescriber Information for Lariam®;
Lariam® Medication Guide; Literature review.

Introduction:
NDA 19-591 (Tablets) was approved by the FDA on May 2, 1989. The most recent approved labeling change for the Lariam® Prescriber Information and Lariam® Medication Guide occurred on August 20, 2003. The sponsor has submitted a revised draft label that includes a new adverse event, pneumonitis of possible allergic etiology, which was observed in postmarket data.

Literature Review
Mefloquine hydrochloride is widely used for the prophylaxis and treatment of malaria. A search of PubMed revealed five case reports in adults of mefloquine-induced pneumonitis. One of the patients (case no. 3) developed a second episode of pneumonitis following a re-challenge with mefloquine. The cases are summarized below.

Case 1 (Greece): A 67 year old female was admitted to hospital with a fever of 39°C, malaise, productive cough, dyspnea on exertion, and peripheral blood eosinophilia. Her medications included mefloquine and ketoconazole shampoo; both were discontinued on admission. The patient had taken mefloquine for 8 weeks during a trip to S. Arica and for 4 weeks on her return. The patient was hypoxemic (PaO_2: 59.5mmHg) on admission. High-resolution chest CT showed bilateral diffuse airspace consolidation and ground-glass attenuation and interlobular septal thickening. Evaluation for infection including tuberculosis and HIV were negative. Laboratory blood tests showed leukocytosis, increased C-reactive protein (CRP), and increased LDH. Serological tests for autoimmune disease were negative. The patient improved with discontinuation of mefloquine. BAL fluid cell count contained 48.5% contained eosinophils (normal < 1%) and in a transbronchial biopsy the alveolar spaces were filled with eosinophils. No mention is made in the report of how the patient was managed during her admission. Topical ketoconazole was restarted without recurrence of symptoms, and a re-challenge with mefloquine was not attempted. The patient improved within a week and was discharged in a few weeks. Follow-up high resolution CT showed significant improvement in lung with minimal residual subpleural infiltrates remaining.[1]

Case 2 (Japan): The second case is from Japan. A summary abstract in English was available for this case. A 59-year-old man took mefloquine, total dose of 1,000 mg, to prevent malaria before and during travel to South Africa. Three weeks after the first administration, he was admitted complaining of fever and dyspnea. Chest high resolution chest CT showed ground-glass opacities and consolidation in both lung fields. Withdrawal of mefloquine and treatment with corticosteroid resulted in improvement of the clinical findings.[2]

[1] Katsenos *et al*. Mefloquine-Induced Eosinophilic Pneumonia. Pharmacotherapy, 2007;27(12):1767-1771
[2] Inoue *et al*. Case of Drug-Induced Pneumonia Possibly due to Mefloquine (antimalarial drug). Nihon Kokyuki Gakkai Zasshi, 2005;43(2):103-7

Case 3 (Belgium): A 60 year old Caucasian female took mefloquine for 3 weeks prior to a visit to Kenya. Her medications included aspirin (atherosclerosis), bisoprolol fumarate (hypertension), and ciprofibratum (hyperlipidemia). After the first dose of mefloquine she developed fever, and chills. And four days later the patient was admitted with fever of 38.5°C, shortness of breath, cyanosis, non productive cough, myalgia, and headaches. Evaluations for an infectious etiology, including tuberculosis and HIV, were negative. Laboratory blood tests showed leukocytosis, increased C-reactive protein (CRP), and increased LDH. A chest x-ray showed bilateral interstitial infiltrates. And the patient was discharged a few weeks later with a diagnosis of diffuse interstitial pneumonia of unknown etiology. Four months later the patient self- started mefloquine before traveling to Kenya. On re-challenge with mefloquine the patient became severely ill with high fever, and respiratory distress requiring admission to ICU. Investigations showed similar results (leukocytosis, a raised CRP, and elevated LDH). There was severe hypoxemia (PaO_2: 45mm Hg, pCO_2: 32 mm Hg, pH: 7.44) on arterial blood gas analysis. High resolution computed tomography (HRCT) showed diffuse pulmonary infiltration and ground-glass attenuation. All the microbiological investigations were negative. The patient responded well clinically and radiologically to treatment with corticosteroids.[3]

Case 4: Drent *et al.* described a case of acute lung injury due to prophylactic mefloquine (total dose of 1,000 mg) in a 64-year-old patient with hemizygote glucose-phosphate dehydrogenase deficiency (G6PD). The patient became dyspneic and febrile two days after taking mefloquine. Chest radiograph showed diffuse nonspecific interstitial infiltrates and lung CT showed diffuse opacities of ground-glass attenuation. All cultures remained sterile and transbronchial lung biopsy revealed diffuse alveolar damage (DAD). The patient was treated with systemic corticosteroids and recovered completely. This patient was reported to have hemizygote deficiency of glucose-phosphate dehydrogenase. The author hypothesized that the severe lung injury resulted from a failure to induce glutathione redox cycle enzyme and from oxidative stress. The author notes this case as the first report of mefloquine-induced pulmonary toxicity reported in the literature. [4]

Case 5 (Switzerland): Udry *et al.* described a case of acute lung injury possibly due to mefloquine. A 53-year- old male patient was treated with a full-day course of therapeutic mefloquine (total dose of 1,500 mg) before admission for a low-level infection (parasitemia = 0.2%) with *Plasmodium falciparum* which was still persistent at one week after self-treatment with halofantrine. The patient received 1,500mg of mefloquine over 24 hours and then developed fever, cough, and dyspnea. He was admitted to the hospital with temperature 38°C, leukocytosis, elevated CRP, elevated LDH, and hypoxemia (PaO2:47mmHg). Hepatic and renal function was normal. A glucose-6-phosphate dehydrogenase level was normal. There was no evidence to suggest a toxin exposure. Computed tomography (CT) confirmed the presence of diffuse bilateral pulmonary infiltrates of ground-glass attenuation and mild thickening of interlobular septa. A BAL

[3] Soentjens *et al*. Mefloquine-Induced Pneumonitis. J. Travel Medicine, 2006;13(3):172-174
[4] Drent M. Drug-induced pneumonia associated with hemizygote glucose-6-phosphate-dehydrogenase deficiency . Eur J Haematol 1998 ; 61 : 218 – 220 .

sample did not show eosinophils and was negative for PCP and other bacterial and fungal pathogens. A video-assisted thoracoscopic (VATS) lung biopsy showed diffuse alveolar damage (DAD).[5]

The case was confounded because acute lung injury can occur due to malaria; however, the authors state that, although acute lung injury can occur secondary to malaria, it typically occurs only in the more severe forms of the disease and usually not in a patient with a low parasitemia who improves rapidly on treatment. Medications before admission included halofantrine, paracetamol, mefloquine. Quinine, doxycycline and ceftriaxone were administered in the hospital. Mefloquine and paracetamol were the only medications that had a temporal relation with the patient's respiratory symptoms.

Medical Officer's Comment

Mefloquine has not been previously associated with drug-induced eosinophilic lung disease or pneumonitis.[6] The first reported case was in 1998 and the most recent case in 2007. The five cases reported in PubMed illustrate that pneumonitis is a rare but serious side effect associated with mefloquine. There was a temporal relationship with mefloquine use and the development of pneumonitis in these cases. One of the patients (case no. 3) had a recurrence of the same symptoms following a re-challenge with mefloquine. An infectious etiology was unlikely in these cases and I find them to be convincing cases of mefloquine-associated pneumonitis. It is important that clinicians are aware of this rare but serious adverse event to prevent delay in diagnosis and appropriate treatment of patients.

Summary of Safety Consult

A consult was sent to DDRE on 01/07/08 for a review of reports of pneumonitis/eosinophilic pneumonitis possibly associated with mefloquine. The final safety review is pending sign-off but a draft review (OSE RCM#2008-28) by S. Christopher Jones, Pharm. D. MS. was provided to the DSPTP on 3/24/2008.

The safety reviewer found the same five cases of probable mefloquine-associated pneumonitis in PubMed that are included in the DSPTP clinical review. Twenty-four AERS cases of pulmonary adverse events associated with mefloquine are summarized, in the safety review, Appendix I. Clinical details from ten supporting cases were provided in the safety review in Appendix II. The majority of the reports were foreign (n=3 US, n=7 non-US). There was a lot of variation in the quality of the clinical details in the cases. All the patients were hospitalized with various respiratory diagnoses that included pneumonitis, diffuse interstitial pneumopathy, and dyspnea/lung infiltration. For these 10 cases, the reporters believed the events to be related to mefloquine or sufficient details were provided to establish a temporal association between drug administration and event onset.

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[5] Udry E , Bailly F , Dusmet M , et al . Pulmonary toxicity with mefloquine . Eur Respir J 2001 ; 18 : 890-892.

[6] Allen JN. Drug-induced eosinophilic lung disease. Clin Chest Med 2004; 25: 77-88.

Four of the ten patients developed pneumonitis while taking mefloquine for prophylaxis,. Another four patients received mefloquine for treatment of malaria and these cases were very difficult to assess because pulmonary symptoms and signs possibly associated with malaria confounded an evaluation for a possible mefloquine-associated pulmonary adverse event. In two cases the indication for mefloquine was not stated. Most patients fully recovered upon discontinuing the presumed offending agent and most patients improved with corticosteroid therapy. However, among the four cases of mefloquine prophylaxis, there was one death in a four-year-old female with no prior medical history who developed pulmonary fibrosis and interstitial pneumonitis and eventually died after several prophylactic doses of mefloquine.

Dr. Jones's recommendation is as follows: "*Findings from the AERS cases and literature review in this consult suggest that pneumonitis or eosinophilic pneumonitis may occur with both mefloquine treatment and prophylactic dosing regimens. These pulmonary adverse events are most likely rare as a broad AERS search only retrieved 24 potential events reported since the drug was first approved in 1989. However, when events have been reported, they do not occur in a predictable fashion and may be difficult to recognize as a drug induced event. Because the current labeling does not contain information based on these post marketing observations, this could potentially delay health care provider recognition of a mefloquine induced pulmonary adverse event. Considering the current AERS data, the published literature, and the serious nature of the events, there appears to be no downside risk to modify the label to more adequately alert prescribers. Therefore, the safety evaluator concurs with the firm's recommend labeling changes.*"

Medical Officer Review of Lariam® Prescriber Information

The following review contains proposed revisions to the current Lariam® Prescriber Information and the Medication Guide for mefloquine hydrochloride. Revisions proposed by the sponsor to the POSTMARKETING and Overdosage sections are as follows:

~~Strikethrough =~~ deleted text
Double underline = added text by Sponsor

ADVERSE REACTIONS

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

Respiratory Disorders: dyspnea, pneumonitis of possible allergic etiology

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

OVERDOSAGE

Symptoms and Signs

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

Treatment

~~The following procedure is recommended in cases of overdosage: Induce vomiting or perform gastric lavage, as appropriate.~~ Patients should be managed by symptomatic and supportive care following Lariam overdose. There are no specific antidotes. 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.

Medical Officer's Comment

*The sponsor's proposed revisions to **ADVERSE REACTIONS, Postmarketing section** of the current Lariam® Prescriber Information are appropriate based on the small number of cases of pneumonitis/eosinophilic pneumonia that appear to be related to mefloquine*

*use. There is no substantial change to the section on **OVERDOSAGE**, **Treatment** as symptomatic and supportive care could include induction of vomiting or gastric lavage. Information on the lack of an antidote for mefloquine overdosage is useful clinical information for health care providers.*

Medical Officer's Recommendation

The sponsor's proposed changed to the **ADVERSE REACTIONS, Postmarketing** subsection and the **OVERDOSAGE, Treatment** subsection are acceptable and can be approved.

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/s/

Elizabeth OShaughnessy
3/31/2008 03:26:18 PM
MEDICAL OFFICER

Joette Meyer
3/31/2008 03:30:08 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-023

OTHER REVIEW(S)

DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS
PM LABELING REVIEW

NDA #:	19-591/S-023
Drug Name:	Lariam® (mefloquine hydrochloride) Tablets, 250 mg
Sponsor:	Hoffman LaRoche, Inc.
Submission date:	November 9, 2007
Receipt date:	November 13, 2007
Reviewer:	Kristen Miller, Pharm.D.

Sponsor: Hoffman LaRoche, Inc.

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

Materials Reviewed:

SLR	Date submitted	Date received
023	November 9, 2007	November 13, 2007

Background:

NDA 19-591 (Tablets) was originally approved on May 2, 1989. The last labeling change for the Lariam® package insert occurred on August 20, 2003. No other labeling changes have been approved since that time.

Supplement 023 was submitted for prior approval and provided for the addition of new information to the **ADVERSE REACTIONS/Postmarketing** subsection and the **OVERDOSAGE** section of the Lariam labeling to include information on pneumonitis, of possible allergic etiology, which was observed in post-market data.

Labeling comparison:

The approved package insert for Lariam dated August 20, 2003 was compared to the proposed package insert dated November 9, 2007. The changes were as follows:

~~Strikethrough~~=deleted text
Double underline=added text

1. The following was added alphabetically under "Other infrequent adverse events include:" in the **ADVERSE REACTIONS/Postmarketing** subsection

   Respiratory Disorders: dyspnea, pneumonitis of possible allergic etiology

2. The **OVERDOSAGE** section was modified as follows:

Symptoms and Signs

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

Treatment

~~The following procedure is recommended in case of overdosage: Induce vomiting or perform gastric lavage, as appropriate.~~ Patients should be managed by symptomatic and supportive care following Lariam overdose. There are no specific antidotes. 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.

Conclusions/Recommendations:

These labeling changes are acceptable. According to the Medical Officer Review by Elizabeth O'Shaughnessy, M.D. dated March 31, 2008, the sponsor's proposed changed to the **ADVERSE REACTIONS/ Postmarketing** subsection and the **OVERDOSAGE** section are acceptable and can be approved.

An approval letter should be sent advising the applicant that this supplemental NDA submission is approved.

Kristen Miller, Pharm. D.
Regulatory Safety Project Manager

Diana Willard
Chief, Project Management Staff

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

/s/

Kristen Miller
5/1/2008 07:54:18 AM
CSO

Diana Willard
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CSO
NDA 19-591/S-023 Project Manager Labeling Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-023

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Surveillance and Epidemiology - Division of Drug Risk and Evaluation

FROM: Division of Special Pathogen and Transplant Products
Kristen Miller, Regulatory Project Manager (301) 796-0762

DATE	IND NO.	SNDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 7, 2008	N/A	19-591/S-023	literature	

NAME OF DRUGS	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lariam (mefloquine)	Standard	Antimalarial	February 19, 2008

NAME OF FIRM: Roche

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: SLR 19-591/S-023 proposes revisions to the labeling regarding pneumonitis/eosinophilic pneumonia. Three cases have been found in the literature (listed below). We are interested to know if there have been additional cases reported in AERS.

Thank you for your assistance with our review. Please let Elizabeth O'Shaughnessy or me know if you have any questions regarding this request. Thank you!

1. Katsenos *et al*. Mefloquine-Induced Eosinophilic Pneumonia. Pharmacotherapy, 2007;27(12):1767-1771

2. Soentjens *et al*. Mefloquine-Induced Pneumonitis. J. Travel Medicine, 2006;13(3):172-174

3. Inoue *et al*. Case of Drug-Induced Pneumonia Possibly due to Mefloquine (antimalarial drug). Nihon Kokyuki Gakkai Zasshi, 2005;43(2):103-7

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kristen Miller, Pharm.D.	■ eMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kristen Miller
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