CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 019591/S-026&028

Trade Name:	Lariam for oral use, 250mg
Generic or Proper Name:	Mefloquine Hydrochloride
Sponsor:	Hoffman-LaRoche, Inc.
Approval Date:	August 20, 2009
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-026&028
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-026&028

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-026
NDA 19-591/S-028

Hoffmann-La Roche Inc.
Attention: Ms. Lynn DeVenezia-Tobias
Senior Program Manager, Diversified Products
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your New Drug Application (NDA) for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

A. Approval of Labeling Supplement

Please also refer to your supplemental new drug application, NDA 19-591/S-026, dated November 19, 2008 and received November 20, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We acknowledge receipt of your submissions dated March 31, 2009, May 26, 2009, July 2, 2009 and August 3, 2009.

This supplemental new drug application provides for revisions to the **CLINICAL PHARMACOLOGY**, **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections of the package insert as well as to the Medication Guide to update information regarding ketoconazole drug interaction, to add information on CYP3A4 and mefloquine metabolism, and to add information regarding an adverse event (vertigo) reported after discontinuation of Lariam as follows (~~strikethrough~~ = deletion and <u>double underlined</u> = addition):

1. The **CLINICAL PHARMACOLOGY/ Pharmacokinetics** subsection has been revised as follows:

   Metabolism
   <u>Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved.</u>

   Two metabolites <u>of mefloquine</u> 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 <u>of the metabolite,</u> 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.

2. The **WARNINGS** section has been revised as follows:

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following co-administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and PRECAUTIONS: Drug Interactions).

~~**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).**~~

3. The **PRECAUTIONS/Central and Peripheral Nervous System Effects** subsection has been revised as follows:

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 or vertigo, 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. In a small number of patients, dizziness or vertigo and loss of balance have been reported to continue for months after discontinuation of the drug ~~mefloquine has been stopped~~ (see **ADVERSE REACTIONS: Postmarketing**).

4. The **PRECAUTIONS/Information for Patients** subsection has been revised as follows:

- that in a small percentage of cases, patients are unable to take this medication because of side effects, including dizziness or vertigo and loss of balance, and it may be necessary to change medications. Although side effects of dizziness or vertigo and loss of balance are usually mild and do not cause people to stop taking the medication, in a small number of patients it has been reported that these symptoms may continue for months after discontinuation of the drug;

5. The **PRECAUTIONS/Drug Interactions** subsection has been revised as follows:

Halofantrine and Other Antimalarials
Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to ~~Because of~~ the risk ~~danger~~ of a potentially fatal prolongation of the QTc interval~~,~~ ~~halofantrine must not be given during Lariam therapy or within 15 weeks after the last dose of simultaneously with or subsequent to Lariam~~ (see **WARNINGS**).

Concomitant administration of Lariam and other related antimalarial 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 QTc interval.~~ Clinically significant QTc prolongation has not been found with mefloquine alone.

Ketoconazole (potent inhibitor of CYP3A4)
Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in a increase in the mean Cmax and AUC of mefloquine by 64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. (see **WARNINGS**)

Other Drugs that Prolong the QTc Interval
~~This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically, c~~Co-administration 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.

Anticonvulsants
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**).

Vaccines
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.~~

Rifampin (Potent Inducer of CYP3A4)
Co-administration of a single 500 mg oral dose of Lariam and 600 mg of rifampin once daily for 7 days in 7 healthy Thai volunteers resulted in a decrease in the mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

Inhibitors and Inducers of CYP3A4

Mefloquine does not inhibit or induce the CYP 450 enzyme system. Thus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers may increase or decrease mefloquine plasma concentrations, respectively.

Substrates and Inhibitors of P-glycoprotein

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

Other Potential Interactions

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

6. The **ADVERSE REACTIONS/Postmarketing** subsection has been revised as follows:

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 swings ~~changes~~, panic attacks, memory impairment ~~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 less frequently reported ~~infrequent~~ adverse events include:

Cardiovascular Disorders: circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular heart rate ~~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, hyperhidrosis ~~sweating~~, chills, dyspepsia and loss of appetite

7. The **ADVERSE REACTIONS/Laboratory** subsection has been revised as follows:

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

8. The Medication Guide has been revised to incorporate additional safety information included in labeling and is located at the end of the Package Insert.

We completed our review of this supplemental application, NDA 19-591/S-026, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

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

B. Approval of Risk Evaluation and Mitigation Strategy (REMS)

Please also refer to your supplemental new drug application, NDA 19-591/S-028, dated May 14, 2009, and received May 15, 2009, under section 505(b) of the FDCA.

We acknowledge receipt of your submissions dated June 30, 2009 and July 24, 2009.

This supplemental new drug application provides for a proposed Risk Evaluation and Mitigation Strategy (REMS), as described below. The proposed REMS includes the revised Medication Guide included in NDA 19-591/S-026.

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Lariam® (mefloquine hydrochloride) was approved on May 2, 1989, we have become aware of a serious risk resulting from an interaction between Lariam® (mefloquine hydrochloride) and ketoconazole, based on our review of peer-reviewed medical literature.[1] Due to the increased plasma concentration and elimination half-life of Lariam® (mefloquine hydrochloride) following co-administration with ketoconazole, the risk of QTc prolongation is increased if ketoconazole is taken during Lariam® (mefloquine hydrochloride) therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of Lariam® (mefloquine hydrochloride). Therefore, we consider this information to be "new safety information" as defined in FDAAA.

Your proposed REMS, submitted on July 24, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

[1] Ridtitid K. et al. Ketoconazole increases plasma concentrations of antimalarial mefloquine in healthyvolunteers. J Clin Pharm Ther 2005; 30:285-90.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Lariam® (mefloquine hydrochloride)
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 19-591 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 19-591
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 19-591
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

CONTENT OF LABELING

As soon as possible, but no later than one month from the date of this letter, please submit the 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 for the package insert and Medication Guide). 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-026**."

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

Please note that you must comply with the Medication Guide Regulations as specified in 21 CFR 208.24. In particular, the carton and container labels must comply with 21 CFR 208.24 (d). Please submit proposed labels for review within 30 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

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
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Package Insert
REMS

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

/s/

OZLEM A BELEN
08/20/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-026&028

LABELING

LARIAM®

brand of

mefloquine hydrochloride

TABLETS

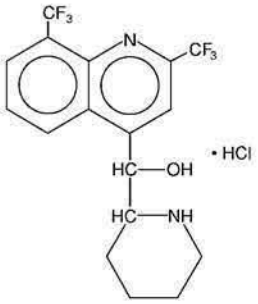
R_X ONLY

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

Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved.

Two metabolites of mefloquine have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive 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 of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

Elimination

In several studies in healthy adults, the mean elimination half-life of mefloquine varied between 2 and 4 weeks, with an average of about 3 weeks. Total clearance, which is essentially hepatic, is in the order of 30 mL/min. There is evidence that mefloquine is excreted mainly in the bile and feces. In volunteers, urinary excretion of unchanged mefloquine and its main metabolite 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.

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following co-administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and 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

Hypersensitivity Reactions

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**).

Central and Peripheral Nervous System Effects

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 or vertigo, 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. In a small number of patients, dizziness or vertigo and loss of balance have been reported to continue for months after discontinuation of the drug (see **ADVERSE REACTIONS:** **Postmarketing**).

Lariam should be used with caution in patients with psychiatric disturbances because mefloquine use has been associated with emotional disturbances (see **ADVERSE REACTIONS**).

Use in Patients with Hepatic Impairment

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

Long-Term Use

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.

Cardiac Effects

Parenteral studies in animals show that mefloquine, a myocardial depressant, possesses 20% of the anti-fibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of mefloquine on the compromised cardiovascular system has not been evaluated. However, transitory and clinically silent ECG alterations have been reported during the use of mefloquine. Alterations included sinus bradycardia, sinus arrhythmia, first degree AV-block, prolongation of the QTc interval and abnormal T waves (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, including dizziness or vertigo and loss of balance, and it may be necessary to change medications. Although side effects of dizziness or vertigo and loss of balance are usually mild and do not cause people to stop taking the medication, in a small number of patients it has been reported that these symptoms may continue for months after discontinuation of the drug;
- 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: Cardiac Effects**). 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.

Halofantrine and Other Antimalarials

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see **WARNINGS**).

Concomitant administration of Lariam and other related antimalarial 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. Clinically significant QTc prolongation has not been found with mefloquine alone.

Ketoconazole (Potent Inhibitor of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in an increase in the mean Cmax and AUC of mefloquine by

64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see **WARNINGS**).

Other Drugs that Prolong the QTc Interval

Co-administration 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.

Anticonvulsants

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**).

Vaccines

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.

Rifampin (Potent Inducer of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam and 600 mg of rifampin once daily for 7 days in 7 healthy Thai volunteers resulted in a decrease in the mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

Inhibitors and Inducers of CYP3A4

Mefloquine does not inhibit or induce the CYP 450 enzyme system. Thus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers may increase or decrease mefloquine plasma concentrations, respectively.

Substrates and Inhibitors of P-glycoprotein

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

Other Potential Interactions

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

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. Because these experiences are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Lariam exposure.

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

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 swings, panic attacks, memory impairment, 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 less frequently reported adverse events include:

Cardiovascular Disorders: circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular heart rate, 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, hyperhidrosis, 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 discontinuation of the drug.

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 pediatric patients weighing less than 20 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 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

Experience with Lariam in pediatric patients weighing less than 20 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.

Revised: Month/Year

MEDICATION GUIDE

Lariam (LAH-ree-am)

(mefloquine hydrochloride)
Tablets

Read this entire Medication Guide before you start taking Lariam and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

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

Your doctor or pharmacist will give you an Information Wallet Card along with this Medication Guide. It has important information about Lariam and should be carried with you at all times while you take Lariam.

Lariam can cause serious mental problems.

- Some people who take Lariam have sudden serious mental problems, including:
  - severe anxiety
  - paranoia (feelings of mistrust towards others)
  - hallucinations (seeing or hearing things that are not there)
  - depression
  - feeling restless
  - unusual behavior
  - feeling confused

In some patients these serious side effects can go on after Lariam is stopped.

- Some people who take Lariam think about suicide (putting an end to their life). Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

  If you have any of these serious mental problems, or you develop other serious side effects or mental problems, you should call your doctor right away as it may be necessary to stop taking Lariam and use another medicine to prevent malaria.

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

If you are told by a doctor to stop taking Lariam because of the side effects or for other reasons, you will need to take another malaria medicine.

If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine for another 4 weeks.

- Do not take halofantrine (used to treat malaria) or ketoconazole (used for fungal infections) with Lariam or within 15 weeks of your last dose of Lariam. You may have serious heart problems that can lead to death. Do not take quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat) with Lariam. You may have serious heart problems.
- Do not take quinine (Qualaquin) or chloroquine (Aralen) (used to treat malaria) with Lariam. You may have a greater risk for convulsions (seizures).

What is Lariam?

Lariam is a prescription medicine used to prevent and treat malaria. Malaria can be a life-threatening infection. Lariam does not work for all types of malaria.

It is not known if Lariam is safe and effective in children under 6 months old for the treatment of malaria.

It is not known how well Lariam works to prevent malaria in infants weighing less than 44 lbs (20 kg).

Who should not take Lariam?

Do not take Lariam if you have:
- depression or had depression recently
- had recent mental problems, including anxiety disorder, schizophrenia, or psychosis (losing touch with reality)
- seizures or had seizures (epilepsy or convulsions)
- an allergy to quinine, quinidine, Lariam or any ingredients in Lariam. See the end of this Medication Guide for a complete list of ingredients in Lariam.

Talk to your doctor before you take Lariam if you have any of the conditions listed above.

What should I tell my doctor before taking Lariam?

Before taking Lariam, tell your doctor about all your medical conditions, including if you have:
- heart disease
- liver problems
- seizures or epilepsy
- diabetes
- blood clotting problems or take blood thinner medicines (anticoagulants)
- mental problems
- are pregnant or plan to become pregnant. It is not known if Lariam will harm your unborn baby. Talk to you doctor if you are pregnant or plan to become pregnant.

- use birth control while you take Lariam and for 3 months after you stop Lariam. If you have an unplanned pregnancy, talk to your doctor right away.
- are breast-feeding or plan to breast-feed. Lariam can pass through your milk and may harm your baby. Ask your doctor whether you will need to stop breast-feeding or use another medicine.

After leaving a malaria area, if you have a fever contact your doctor right away.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lariam and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Especially tell your doctor if you take:
- ketoconazole used to treat fungal infections
- halofantrine, quinine (Qualaquin), quinidine, chloroquine (Aralen) or other medicines used to treat malaria
- anti-arrhythmic medicines, beta-adrenergic blocking medicines and calcium channel blockers used to treat heart problems or high blood pressure
- antihistamines or H_1-blocking agents used to treat allergies
- tricyclic antidepressants used to treat depression
- phenothiazines used to treat mental problems
- anticonvulsants used to treat seizures
- vaccines containing live bacteria. Your doctor may want you to finish receiving your vaccines at least 3 days before you start Lariam.
- rifampin and rifampin-containing products (Rifadin, Rifamate, Rifater, Rimactane) used to treat infections

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

How should I take Lariam?

- Take Lariam exactly as your doctor tells you to take it. Your doctor will tell you how many Lariam to take and when to take them.
- You will start taking Lariam to prevent malaria between 1 to 3 weeks before you travel to a malaria area.
- Take Lariam just after eating your main meal and with at least one cup (8 ounces) of water.
- Do not take Lariam on an empty stomach.
- If you vomit after taking Lariam, call your healthcare provider to see if you should take another dose.
- Continue taking Lariam for 4 weeks after returning from a malaria area**.**
- Lariam tablets may be crushed and mixed with a small amount of water, milk or other beverage for children or other people unable to swallow Lariam whole. Your doctor will tell you the correct dose for your child based on your child's weight.
- If you take Lariam for a year or longer, your doctor should check your
    - eyes, especially if you have trouble seeing while you take Lariam
    - liver function to see if there has been damage to your liver

- Use protective clothing, insect repellents, and bednets to protect you from being bitten by mosquitoes. Medicine alone does not always stop you from catching malaria from mosquito bites.

What should I avoid while taking Lariam?

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you. You may feel dizzy or lose your balance. This could happen for months after you stop taking Lariam. See "What are the possible side effects of Lariam?"

What are the possible side effects of Lariam?

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

Lariam may cause serious side effects, including:

- convulsions (seizures)
- liver problems
- heart problems

The most common side effects of Lariam include:

- nausea
- vomiting
- diarrhea
- abdominal pain
- dizziness or loss of balance (vertigo), which may continue for months after Lariam is stopped
- headache
- sleeping problems (sleepiness, unable to sleep, bad dreams)

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

- muscle pain
- fever
- chills
- skin rash
- fatigue
- loss of appetite
- ringing in the ears
- irregular heart beat

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lariam. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lariam?

- Store Lariam between 59ºF to 86ºF (15ºC to 30ºC)
- Safely throw away medicine that is out of date or no longer needed.

Keep Lariam and all medicines out of the reach of children.

General information about the safe and effective use of Lariam.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lariam for a condition for which it was not prescribed. Do not give Lariam to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Lariam. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lariam that is written for health professionals.

If you have any questions or would like more information about Lariam, you can call Roche, the manufacturer of Lariam, at 1-800-526-6367.

What are the ingredients in Lariam?

Active ingredients: mefloquine hydrochloride

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

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

Reprint of information wallet card:

Information Wallet Card

Lariam® (mefloquine hydrochloride) Tablets

It is important that you read the entire Medication Guide for additional information on Lariam.

Carry this 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.

Lariam can cause serious mental problems in some people. If you take Lariam and you have sudden signs of serious mental problems (such as: severe anxiety, feelings of mistrust towards others, seeing or hearing things that are not there, depression, feeling restless, unusual behavior or feeling confused), you should contact a doctor right away as it may be necessary to stop taking Lariam and take different medicine to prevent malaria.

Other side effects from Lariam may include: convulsions, liver problems, and heart problems. The most common side effects of Lariam include nausea, vomiting, diarrhea, abdominal pain, dizziness or loss of balance (vertigo) which may continue for months after Lariam is stopped, headache, and sleeping problems (sleepiness, unable to sleep, bad dreams).

While you take Lariam, do not take:

- **Halofantrine (used to treat malaria)**
- **Ketoconazole (used for fungal infections)**
- **Quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat)**
- **Chloroquine (Aralen) (used to treat malaria)**

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you.

Other medicines are approved in the United States for malaria prevention. However, not all malaria medicines work equally well in different malaria areas. Before you travel, talk to your doctor about your travel plans.

If you have any serious side effects, and cannot get another medicine, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

Card Revised: Month/Year

Manufactured by:

F. HOFFMANN-LA ROCHE LTD
Basel, Switzerland

Distributed by:

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

Revised: Month/Year

LMT_215998_MG_MMYYYY_N

Appendix A: Medication Guide REMS Document

NDA 19-591 Lariam® (mefloquine hydrochloride) Tablets

Antimalarial Agent for the Treatment and Prevention of Malaria

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
Roche Pharmaceuticals Service Center Telephone Contact Number:
1-800-526-6367

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL: To inform patients about the serious risks associated with the use of Lariam (mefloquine hydrochloride).

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each Lariam prescription in accordance with 21 CFR 208.

Pursuant to 21 CFR 208.24, the Medication Guide will be made available in sufficient numbers to US Lariam distributors. US distributors will provide the Medication Guide with every pharmacy shelf carton of Lariam to ensure its availability for dispensing to patients who are dispensed Lariam. The label of each container or package of Lariam will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided.

See appended Medication Guide.

B. Timetable for Submission of Assessments

The timetable for submission of assessments of the REMS will be 18 months, 3 years, and 7^{th} years after the REMS is initially approved. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment.

MEDICATION GUIDE

Lariam (LAH-ree-am)

(mefloquine hydrochloride)
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- Some people who take Lariam have sudden serious mental problems, including:
  - severe anxiety
  - paranoia (feelings of mistrust towards others)
  - hallucinations (seeing or hearing things that are not there)
  - depression
  - feeling restless
  - unusual behavior
  - feeling confused

In some patients these serious side effects can go on after Lariam is stopped.

- Some people who take Lariam think about suicide (putting an end to their life). Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

  If you have any of these serious mental problems, or you develop other serious side effects or mental problems, you should call your doctor right away as it may be necessary to stop taking Lariam and use another medicine to prevent malaria.

  You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area. If you are told by a doctor to stop taking Lariam because of the side effects or for other reasons, you will need to take another malaria medicine.

  If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area and contact a doctor as soon as possible because leaving

the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine for another 4 weeks.

- Do not take halofantrine (used to treat malaria) or ketoconazole (used for fungal infections) with Lariam or within 15 weeks of your last dose of Lariam. You may have serious heart problems that can lead to death. Do not take quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat) with Lariam. You may have serious heart problems.
- Do not take quinine (Qualaquin) or chloroquine (Aralen) (used to treat malaria) with Lariam. You may have a greater risk for convulsions (seizures).

What is Lariam?

Lariam is a prescription medicine used to prevent and treat malaria. Malaria can be a life-threatening infection. Lariam does not work for all types of malaria.

It is not known if Lariam is safe and effective in children under 6 months old for the treatment of malaria.

It is not known how well Lariam works to prevent malaria in infants weighing less than 44 lbs (20 kg).

Who should not take Lariam?

Do not take Lariam if you have:
- depression or had depression recently
- had recent mental problems, including anxiety disorder, schizophrenia, or psychosis (losing touch with reality)
- seizures or had seizures (epilepsy or convulsions)
- an allergy to quinine, quinidine, Lariam or any ingredients in Lariam. See the end of this Medication Guide for a complete list of ingredients in Lariam.

Talk to your doctor before you take Lariam if you have any of the conditions listed above.

What should I tell my doctor before taking Lariam?

Before taking Lariam, tell your doctor about all your medical conditions, including if you have:
- heart disease
- liver problems
- seizures or epilepsy
- diabetes
- blood clotting problems or take blood thinner medicines (anticoagulants)
- mental problems
- are pregnant or plan to become pregnant. It is not known if Lariam will harm your unborn baby. Talk to you doctor if you are pregnant or plan to become pregnant.
- use birth control while you take Lariam and for 3 months after you stop Lariam. If you have an unplanned pregnancy, talk to your doctor right away.

- are breast-feeding or plan to breast-feed. Lariam can pass through your milk and may harm your baby. Ask your doctor whether you will need to stop breast-feeding or use another medicine.

After leaving a malaria area, if you have a fever contact your doctor right away.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lariam and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Especially tell your doctor if you take:
- ketoconazole used to treat fungal infections
- halofantrine, quinine (Qualaquin), quinidine, chloroquine (Aralen) or other medicines used to treat malaria
- anti-arrhythmic medicines, beta-adrenergic blocking medicines and calcium channel blockers used to treat heart problems or high blood pressure
- antihistamines or H_1-blocking agents used to treat allergies
- tricyclic antidepressants used to treat depression
- phenothiazines used to treat mental problems
- anticonvulsants used to treat seizures
- vaccines containing live bacteria. Your doctor may want you to finish receiving your vaccines at least 3 days before you start Lariam.
- rifampin and rifampin-containing products (Rifadin, Rifamate, Rifater, Rimactane) used to treat infections

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

How should I take Lariam?

- Take Lariam exactly as your doctor tells you to take it. Your doctor will tell you how many Lariam to take and when to take them.
- You will start taking Lariam to prevent malaria between 1 to 3 weeks before you travel to a malaria area.
- Take Lariam just after eating your main meal and with at least one cup (8 ounces) of water.
- Do not take Lariam on an empty stomach.
- If you vomit after taking Lariam, call your healthcare provider to see if you should take another dose.
- Continue taking Lariam for 4 weeks after returning from a malaria area**.**
- Lariam tablets may be crushed and mixed with a small amount of water, milk or other beverage for children or other people unable to swallow Lariam whole. Your doctor will tell you the correct dose for your child based on your child's weight.
- If you take Lariam for a year or longer, your doctor should check your
    - eyes, especially if you have trouble seeing while you take Lariam
    - liver function to see if there has been damage to your liver

- Use protective clothing, insect repellents, and bednets to protect you from being bitten by mosquitoes. Medicine alone does not always stop you from catching malaria from mosquito bites.

What should I avoid while taking Lariam?

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you. You may feel dizzy or lose your balance. This could happen for months after you stop taking Lariam. See "What are the possible side effects of Lariam?"

What are the possible side effects of Lariam?

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

Lariam may cause serious side effects, including:

- convulsions (seizures)
- liver problems
- heart problems

The most common side effects of Lariam include:

- nausea
- vomiting
- diarrhea
- abdominal pain
- dizziness or loss of balance (vertigo), which may continue for months after Lariam is stopped
- headache
- sleeping problems (sleepiness, unable to sleep, bad dreams)

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

- muscle pain
- fever
- chills
- skin rash
- fatigue
- loss of appetite
- ringing in the ears
- irregular heart beat

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lariam. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lariam?

- Store Lariam between 59ºF to 86ºF (15ºC to 30ºC)
- Safely throw away medicine that is out of date or no longer needed.

Keep Lariam and all medicines out of the reach of children.

General information about the safe and effective use of Lariam.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lariam for a condition for which it was not prescribed. Do not give Lariam to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Lariam. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lariam that is written for health professionals.

If you have any questions or would like more information about Lariam, you can call Roche, the manufacturer of Lariam, at 1-800-526-6367.

What are the ingredients in Lariam?

Active ingredients: mefloquine hydrochloride

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

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

Reprint of information wallet card:

Information Wallet Card

Lariam® (mefloquine hydrochloride) Tablets

It is important that you read the entire Medication Guide for additional information on Lariam.

Carry this 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.

Lariam can cause serious mental problems in some people. If you take Lariam and you have sudden signs of serious mental problems (such as: severe anxiety, feelings of mistrust towards others, seeing or hearing things that are not there, depression, feeling restless, unusual behavior or feeling confused), you should contact a doctor right away as it may be necessary to stop taking Lariam and take different medicine to prevent malaria.

Other side effects from Lariam may include: convulsions, liver problems, and heart problems. The most common side effects of Lariam include nausea, vomiting, diarrhea, abdominal pain, dizziness or loss of balance (vertigo) which may continue for months after Lariam is stopped, headache, and sleeping problems (sleepiness, unable to sleep, bad dreams).

While you take Lariam, do not take:

- **Halofantrine (used to treat malaria)**
- **Ketoconazole (used for fungal infections)**
- **Quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat)**
- **Chloroquine (Aralen) (used to treat malaria)**

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you.

Other medicines are approved in the United States for malaria prevention. However, not all malaria medicines work equally well in different malaria areas. Before you travel, talk to your doctor about your travel plans.

If you have any serious side effects, and cannot get another medicine, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

Card Revised: Month/Year

Manufactured by:

F. HOFFMANN-LA ROCHE LTD
Basel, Switzerland

Distributed by:

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

Revised: Month/Year

LMT_215998_MG_MMYYYY_N

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019591/S-026&028

CLINICAL REVIEW(S)

NDA 19-591, S-026

Prior Approval Labeling Supplement: Lariam® Prescriber Information and Lariam® Medication Guide

Submission Dates:	November 19th 2008; March 31st, 2009
Medical Officer:	Elizabeth O'Shaughnessy, M.D.
Acting Team Leader:	Joette Meyer, Pharm. D.
Division Director:	Renata Albrecht, M.D.
Project Manager:	Gregory DiBernardo
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
Indications:	(b) (4)
Material(s) Reviewed:	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 September 23, 2008.

On November 19th, 2008, Hoffman-La Roche submitted a Prior Approval Labeling Supplement for mefloquine, Lariam®. The sponsor submitted a revised draft Prescriber Information (PI) in structured product labeling (SPL) format that includes changes to the following sections: **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS**, and **ADVERSE REACTIONS**, and changes to the **MEDICATION GUIDE**. The sponsor also informed the FDA that they have discontinued the manufacture of Lariam.

Literature references and results of analyses of the sponsor's safety global database and an internal analysis of drug interactions to support the proposed labeling changes were submitted for review. The changes proposed by the sponsor to the Prescriber Information and the Medication Guide are listed below and are summarized with the supporting literature references in Table 1.

Proposed Labeling Changes Include Addition of:

- New information on Mefloquine metabolism by CYP3A4, drug-drug interactions and potential for QT interval prolongation; changes to the label include information on drug-drug interactions between mefloquine and ketoconazole, rifampin, and halofantrine.
- Adverse event (vertigo) reported after discontinuation of mefloquine
- New MedRA terms to describe adverse events
- Minor editorial changes

Table 1. Complete List of the Labeling Changes and Supportive Information for the Proposed Changes

Section	Revision	Explanation
CLINICAL PHARMACOLOGY: Metabolism	Added new statements re: mefloquine metabolism in the liver by the cytochrome P450 system	Literature review/internal analysis of drug-drug interactions and mefloquine metabolism: 1. Ridtitid W, Wongnawa M, Mahatthanatrakul W, et al. Ketoconazole increases plasma concentrations of antimalarial mefloquine in healthy human volunteers. *J Clin Pharm Ther*. 2005;30:285-290. 2. Ridtitid W, Wongnawa M, Mahatthanatrakul W, et al. Effect of rifampin on plasma concentration of mefloquine in healthy volunteers. *J Pharm Pharmacol*. 2000;52:1265-1269. 3. Fontaine F, de Sousa G, Burcham PC, et al. Role of cytochrome P450 3A in the metabolism of mefloquine in human and animal hepatocytes. *Life Sci*. 2000;66(22):2193-2212. 4. Bona V, Bucheli F, Heinig K, et al. Inhibition effect of the antimalarial RO0215998 (mefloquine) on cytochrome P450-specific activities of human liver microsomes. *Roche Report No. 1029476*, 2008.
WARNINGS	Updated information re: QTc prolongation and drug-drug interactions	Literature review/internal analysis: 5. Suter P. Cardiac disorders/SMQ

Section	Revision	Explanation
		torsade de pointes. *Roche Drug Safety Report No. 1028143*, December 7, 2007. 6. Yap YG, Camm AJ. Drug induced QT prolongation and torsade de pointes. *Heart*. 2003;89:1363-1372. 7. Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy*. 2003;23(7):881-908. 8. Schenkel F, Suter P. Interaction between mefloquine and ketoconazole or rifampicin. *Roche Drug Safety Report No. 1028566*, February 2008.
PRECAUTIONS: Central and Peripheral Nervous System Effects	Added information re: in a small number of patients, vertigo has been reported to continue for months after discontinuation of the drug	Internal analysis: 9. Suter P, Adamcova M, Schwarz R, et al. Neurological disorders and ear disorders/vestibular disorders. *Roche Drug Safety Report No. 1030707,* August 22, 2008. Note: this report was submitted to Lariam NDA 19-591 on August 28, 2008.
PRECAUTIONS: Information for Patients	Added "vertigo"	Reference 9
PRECAUTIONS: Drug Interactions	See WARNINGS section above	References 5, 6, 7, and 8
PRECAUTIONS: Other Potential Interactions	Added new section and subsections regarding other potential drug interactions	Literature review: references 1, 2, and the following: 10. Riffkin CD, Chung R, Wall DM, et al. Modulation of the function of human MDR1 P-glycoprotein by the antimalarial drug mefloquine. *Biochem Pharmacol*. 1996;52:1545-1552.
ADVERSE REACTIONS:	Revised terms from "mood	New MedDRA terms

Section	Revision	Explanation
Postmarketing	changes," "forgetfulness," "irregular pulse," and "sweating" to "mood swings," "memory impairment," "irregular heart rate," and "hyperhidrosis," respectively Revised the phrase "other infrequent adverse events" to "other less frequently reported adverse events"	 Editorial
ADVERSE REACTIONS: Last paragraph in section	Revised the sentence "Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist up to several weeks after the last dose" to "Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist up to several weeks after discontinuation of the drug."	Consistent with wording of similar statements in other sections of the label
MEDICATION GUIDE: What should I avoid while taking Lariam ?	(b) (4)	Reference 9
MEDICATION GUIDE: What are the possible side effects of Lariam?	Added "vertigo"	Reference 9
Other	Added new Roche distribution signature	Corporate consistency

Literature references and safety reports (cited in the table above) to support the changes related to the drug-drug interactions with ketoconazole and rifampin, and the possible QTc interval prolongation associated with use of halofantrine and mefloquine and the safety data regarding neurological adverse events were reviewed.

Note: A <u>double underline</u> indicates additional label revisions and ~~double strikethrough~~ indicates removal of text made by the sponsor.

The Sponsor proposed the following changes to the **CLINICAL PHARMACOLOGY** section of the label:

<u>Metabolism</u>

<u>Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved.</u>

Two metabolites of mefloquine 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 of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks.

Clinical Reviewer Comment
No additional changes were proposed in this section by the clinical pharmacology reviewer. The Division agrees with the sponsor's proposed changes to the section.

The Sponsor proposed the following changes to the **WARNINGS** section:

WARNINGS

(b) (4)

~~**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).**~~

Clinical Reviewer Comment:
Both halofantrine and mefloquine have long half-lives, halofantrine is known to prolong the QT interval and the degree of QT prolongation is dependent on the plasma concentration of the drug. Mefloquine affects the QT interval to a lesser extent than halofantrine but there are cases of QT prolongation reported. (b) (4)

In a study published by Nosten et al.,[1] the risk of significant QT prolongation (> 25%) was greater if halofantrine was given as a re-treatment following mefloquine failure than as primary treatment. More than 60% of the effect occurred with three doses

[1] Nosten F., et al. Cardiac Effects of antimalarial treatment with halofantrine. Lancet 1993;341:1113-4.

of halofantrine (24 mg/kg). The known half-life of mefloquine is 13 to 19 days and five times the half-life would be approximately 14 to 15 weeks, therefore the proposed interval of 15 weeks between the two drugs appears appropriate.
Ketoconazole is a potent inhibitor of CYP3A4 and co-administration with mefloquine would be expected to increase mefloquine levels. Ketoconazole was shown to increase plasma mefloquine concentrations in a study in healthy human volunteers.[2] It is appropriate to include a warning regarding the use of mefloquine with halofantrine or ketoconazole (concomitantly and sequentially) as the combination(s) can prolong the QT interval and promote life-threatening cardiac arrhythmias.

A counterproposal from the FDA, (b) (4) was sent via fax to the sponsor on March 12th 2009 and the final agreed upon text was submitted by the sponsor on March 31, 2009 as shown:

WARNINGS

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following co-administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and PRECAUTIONS: Drug Interactions).

The Sponsor proposed the following changes to the **PRECAUTIONS** section:

Central and Peripheral Nervous System Effects

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 or vertigo, 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. In a small number of patients, dizziness or vertigo and loss of balance have been reported to continue for months after ~~**mefloquine has been stopped**~~ discontinuation of the drug (see **ADVERSE REACTIONS: Postmarketing**).

[2] Ridtitid K. et al. Ketoconazole increases plasma concentrations of antimalarial mefloquine in healthy volunteers. J Clin Pharm Ther 2005; 30:285-90

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, including dizziness or vertigo and loss of balance, and it may be necessary to change medications. Although side effects of dizziness or vertigo and loss of balance are usually mild and do not cause people to stop taking the medication, in a small number of patients it has been reported that these symptoms may continue for months after discontinuation of the drug;

Drug Interactions

Because of the ~~danger~~ (b) (4) of a potentially fatal prolongation of the QTc interval, halofantrine must not be given Lariam ~~simultaneously with or subsequent to Lariam~~ (b) (4) 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~~.

(b) (4)

(b) (4)

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

(b) (4)

[redacted]

Substrates and Inhibitors of P-glycoprotein

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

*Please refer to my comments on **WARNINGS** section above regarding halofantrine and ketoconazole interactions.* (b) (4)

[redacted]

Please refer to the review by the clinical pharmacology reviewer, D. Chilukuri, Ph.D., for more detailed review of drug interaction . (b) (4)

[redacted]

A counterproposal was sent from the FDA, in order to include additional information on the interaction with ketoconazole and rifampin, as well as to rearrange the new information in the Drug Interactions subsection of the **PRECAUTIONS**. A fax was sent to the sponsor on March 12th, 2009 and the final agreed upon text for the entire Drug Interactions subsection was submitted by the sponsor on March 31st, 2009 and is included below:

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: Cardiac Effects**). 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.

Halofantrine and Other Antimalarials

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see **WARNINGS**).

Concomitant administration of Lariam and other related antimalarial 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. Clinically significant QTc prolongation has not been found with mefloquine alone.

Ketoconazole (Potent Inhibitor of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in an increase in the mean Cmax and AUC of mefloquine by 64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see **WARNINGS**).

Other Drugs that Prolong the QTc Interval

Co-administration 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.

Anticonvulsants

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**).

Vaccines

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.

Rifampin (Potent Inducer of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam and 600 mg of rifampin once daily for 7 days in 7 healthy Thai volunteers resulted in a decrease in the mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

Inhibitors and Inducers of CYP3A4

Mefloquine does not inhibit or induce the CYP 450 enzyme system. Thus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers may increase or decrease mefloquine plasma concentrations, respectively.

Substrates and Inhibitors of P-glycoprotein

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

Other Potential Interactions

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

The Sponsor proposed the following changes to the **ADVERSE REACTIONS** section:

Postmarketing

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~~ swings, panic attacks, ~~forgetfulness~~ memory impairment, 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~~ less frequently reported adverse events include:

Cardiovascular Disorders: circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular ~~pulse~~ heart rate, 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~~ hyperhidrosis, chills, dyspepsia and loss of appetite

Laboratory

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

Clinical Reviewer's Comment

*The changes to the **ADVERSE REACTIONS** were made in line with new MedRA terminology. The minor change to the Laboratory subsection is also acceptable. The Division agrees with the changes to the **ADVERSE REACTIONS** section.*

The Sponsor proposed the following changes to the **MEDICATION GUIDE**:

(b) (4)

In addition:

- **Be careful driving or in other activities** needing alertness and careful movements (fine motor coordination). Lariam can cause dizziness (b) (4) or loss of balance, even after you stop taking Lariam (see "**What are the possible side effects of Lariam?**").
- **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 or vertigo, loss of balance, difficulty sleeping, and bad dreams. These side effects are usually mild and do not cause people to stop taking the medicine. However, in a small number of patients, it has been reported that dizziness or vertigo and loss of balance may continue for months after stopping 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 or vertigo, loss of balance, difficulty sleeping, and bad dreams. These side effects are usually mild and do not cause people to stop taking the

medicine. However, in a small number of patients, it has been reported that dizziness or vertigo and loss of balance may continue for months after stopping Lariam.

Clinical Reviewer's Comment

In the ADVERSE REACTIONS section of the current Lariam® Prescriber Information and the MEDICATION GUIDE, the adverse event, vertigo, was added to the labeling in the November 19, 2008 submission. Mefloquine is known to cause dizziness and other vestibular adverse effects such as loss of balance and these adverse effects are listed in the current label.

The sponsor's Drug Safety Report No. 1030707 was reviewed with respect to the adverse event of vertigo. Using the preferred term "vertigo" or "vertigo positional," 506 cases of vertigo were recorded globally up to April 2008. The reports are based on voluntary reporting and therefore are probably an underestimate of the actual numbers. Seventeen cases were reported to have vertigo associated with mefloquine with a duration greater than 90 days which was estimated based on the reported onset date of the event and the last report date since the resolution date of the event was unknown. The 17 cases had new/prolonged hospitalization or disability related to vertigo. In 10 of the17 cases vertigo was reported as "persisting" and in seven cases, the outcome was reported as "improved".

The safety data provided by the sponsor from their global safety data base support the addition of vertigo to the drug label.

*The potential drug-drug interaction between ketoconazole and mefloquine was added to the MEDICATION GUIDE in the March xx, 2009 submission appropriately by the sponsor, since new information has been added to the **WARNINGS** section regarding the risk of this interaction. Since new safety information is being added to the MEDICATION GUIDE, a Risk Evaluation and Mitigation Strategy (REMS) is also required along with a review of the complete MEDICATION GUIDE by the Division of Risk Assessment (DRISK) in OSE. Please see review regarding REMS by O. Belen MD, Deputy Director for Safety.*

Clinical Reviewer's Recommendation

The safety data information provided by the sponsor from their global safety data base support the proposed changes in the drug label. The sponsor's proposed changes to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS**, and **ADVERSE REACTIONS** subsections and **MEDICATION GUIDE** are acceptable and I recommend approval.

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/s/

Elizabeth OShaughnessy
4/3/2009 06:42:06 PM
MEDICAL OFFICER

Joette Meyer
4/4/2009 02:05:46 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-026&028

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA/Serial #	19-591/S-026
Brand/Generic	Lariam/Mefloquine
Submission Date	March 31st, 2008
Applicant	Roche
Clinical Division	DSPTP
OCP Division	DCP4
Type of Submission	Prior Approval Supplement
Reviewer	Dakshina Chilukuri, Ph.D.
Team Leader	Philip Colangelo, Pharm D., Ph.D.
Review Date	July 1st, 2009

Executive Summary

NDA 19-591/S-026 was submitted by Roche on December 01, 2008 as a "Prior Approval Supplement". Revisions were proposed to the **CLINICAL PHARMACOLOGY/ Metabolism section,** the **WARNINGS** section**,** the **PRECAUTIONS Central** and **Peripheral Nervous System Effects,** the **PRECAUTIONS/Information** for **Patients**, the **PRECAUTIONS/Drug Interactions**, the **PRECAUTIONS/Other Potential Interactions**, **Postmarketing and Laboratory** sections.

The clinical pharmacology team provided responses to the sponsor's proposal for labeling revisions (see clinical pharmacology review dated 02/25/09). The sponsor subsequently accepted the proposed revisions. In a submission dated 03/31/09, the sponsor submitted a revised label incorporating the agreed-upon changes. This latest version of the label is acceptable and is included in Attachment-1.

Dakshina Chilukuri, Ph.D. _____
Office of Clinical Pharmacology

Initialed by Philip Colangelo, Pharm D., Ph.D. _____
Team Leader, DCP4, Office of Clinical Pharmacology
cc: NDA 19-591 and CDR (Biopharm).

19 Pages Draft Labeling have been Withheld in Full as B4)CCI/TS) Immediately Following this Page

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/s/

Dakshina Chilukuri
7/1/2009 03:39:23 PM
BIOPHARMACEUTICS

Phil Colangelo
7/8/2009 11:58:16 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology Review

NDA/Serial #	19-591/S-026
Brand/Generic	Lariam/Mefloquine
Submission Date	December 01, 2008
Applicant	Roche
Clinical Division	DSPTP
OCP Division	DCP4
Type of Submission	Prior Approval Supplement
Reviewer	Dakshina Chilukuri, Ph.D.
Team Leader	Philip Colangelo, Pharm D., Ph.D.
Review Date	February 25, 2009

Background

NDA 19-591/S-026 was submitted by Roche on December 01, 2008 as a "Prior Approval Supplement". Revisions were proposed to the **CLINICAL PHARMACOLOGY/ Metabolism section,** the **WARNINGS** section**,** the **PRECAUTIONS Central** and **Peripheral Nervous System Effects,** the **PRECAUTIONS/Information** for **Patients**, the **PRECAUTIONS/Drug Interactions**, the **PRECAUTIONS/Other Potential Interactions**, **Postmarketing and Laboratory** sections.

The sponsor submitted several publications in support of the proposed changes. Given below are the proposed changes and clinical pharmacology team's comments:

1. Under **CLINICAL PHARMACOLOGY/ Metabolism,** the following revisions were proposed by the sponsor (sponsor additions indicated as underlined wording):

   Metabolism

   Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved.[1,2,3,4]

   Two metabolites of mefloquine 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 of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

   Reviewer's Comments:

   The sponsor has submitted 3 publications and 1 study report in support of the above-mentioned changes (Ridtitid et. al., J. Clin. Pharmacy and Ther., (2005), 30,

285-290, Ridtitid et. al., J. Pharm. Pharmacol. (2000), 52, 1265-1269, Fontaine et, al., Life Sciences, Vol. 66, No. 22, 2000, 2193-2212 and Bona et. al, Report No. 1029476, Roche Biosciences).. Upon review of the submitted information, it is clear that mefloquine is metabolized by the CYP3A4 enzymes and so the sponsor's wording is acceptable.

2. Under WARNINGS, the following revisions were proposed by the sponsor (sponsor additions indicated as underlined wording):

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.

(b) (4)

Reviewer's Comments:

Clinical Pharmacology revisions to the proposed wording are as follows. FDA changes are given as double underline.

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.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3. **Under DRUG INTERACTIONS, the following revisions were proposed by the sponsor (sponsor additions indicated as <u>underlined</u> wording).**

PRECAUTIONS

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: Cardiac Effects**). 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 (b) (4) of a potentially fatal prolongation of the QTc interval, halofantrine must not be given during <u>Lariam therapy or within 15 weeks after the last dose of Lariam</u> (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.

(b) (4)

Reviewer's Comments:
Clinical Pharmacology revisions to the proposed wording are as follows. FDA changes are given as double underline and/or ~~strikethroughs~~

PRECAUTIONS
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: Cardiac Effects**). 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 (b) (4) of a potentially fatal prolongation of the QTc interval, halofantrine must not be given (b) (4) (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.

(b) (4)

4. **Under DRUG INTERACTIONS, the following revisions were proposed by the sponsor (sponsor additions indicated as underlined wording).**

PRECAUTIONS
(b) (4)

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

(b) (4)

(b) (4)

Substrates and Inhibitors of P-glycoprotein

It has been shown in vitro that mefloquine is a substrate and an inhibitor of P-glycoprotein.[10] Therefore, drug-drug interactions could also occur with drugs that are substrates or are known to modify the expression of this transporter. The clinical relevance of these interactions are not known to date.

Reviewer's Comments:
Clinical Pharmacology revisions to the proposed wording are as follows. FDA changes are given as double underline and/or ~~strikethroughs.~~

5. PRECAUTIONS

Ketoconazole (potent inhibitor of CYP3A4)

(b) (4)

Rifampin (potent inducer of CYP3A4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Substrates and Inhibitors of P-glycoprotein

It has been shown in vitro that mefloquine is a substrate and an inhibitor of P-glycoprotein.[10] Therefore, drug-drug interactions could also occur with drugs that are substrates or are known to modify the expression of this transporter. The clinical relevance of these interactions are not known to date.

Dakshina Chilukuri, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics

Initialed by Philip Colangelo, Pharm D., Ph.D.
Team Leader, DCP4, Office of Clinical Pharmacology and Biopharmaceutics
cc: NDA 19-591 and CDR (Biopharm).

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/s/

Dakshina Chilukuri
2/25/2009 06:04:53 PM
BIOPHARMACEUTICS

Phil Colangelo
2/27/2009 04:52:13 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-026&028

OTHER REVIEW(S)

DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS
Project Management Review of Supplemental Labeling Revisions

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
19-591	Lariam® (mefloquine hydrochloride) Tablets, 250 mg	026	November 19, 2008	November 20, 2008
		028	May 14, 2009	May 15, 2009

Applicant: Hoffmann-La Roche Inc.

Date of Review: August 18, 2009

Documents Reviewed:

S-026
Package Insert

- Original submission NDA 19-591/S-026 dated November 19, 2008
- December 15, 2008 Acknowledgement letter for S-026
- February 27, 2009 Clinical Pharmacology Review of S-026
- March 12, 2009 facsimile transmission (FAX) proposing revisions to the package insert
- March 31, 2009 Labeling Amendment to S-026
- April 4, 2009 Medical Officer Review of the November 19, 2008 and March 31, 2009 Submissions
- Most recent labeling (text for the package insert) approved on June 26, 2009 (NDA 19-591/S-027).
- July 8, 2009 Clinical Pharmacology Review of Submission dated, March 31, 2009

S-026
Medication Guide

- Most recent Medication Guide approved on September 23, 2008 (NDA 19-591/ S-024)
- Original submission NDA 19-591/S-026 dated November 19, 2008
- March 31, 2009 Labeling Amendment to S-026
- April 30, 2009 DRISK Consult Review of Patient Labeling, Medication Guide, and Information Wallet Card
- May 1, 2009 DDMAC Consult Request to Review November 19, 2008 and March 31, 2009 versions of Medication Guide
- May 4, 2009 facsimile transmission proposing revisions to the Medication Guide
- May 26, 2009 Amendment to S-026 regarding the Medication Guide

- June 1, 2009 DRISK Consult Request of May 26, 2009 version of Medication Guide
- June 3, 2009 DDMAC Consult Review of proposed DRISK revisions to Medication Guide
- June 16, 2009 facsimile transmission to propose Medication Guide Revisions
- June 29, 2009 facsimile transmission to propose Medication Guide Revisions, incorporating changes from approval of S-027
- July 2, 2009 Medication Guide Amendment to S-026
- August 3, 2009 Medication Guide Amendment to S-026

S-028
Risk Evaluation and Mitigation Strategy (REMS)

- April 17, 2009 REMS Memo
- April 17, 2009 REMS Request Letter
- Original submission NDA 19-591/S-028 dated May 14, 2009
- DRISK Consult Review of REMS May 14, 2009 Submission
- June 22, 2009 Facsimile transmission regarding May 14, 2009 proposed REMS
- June 30, 2009 Submission regarding Proposed Timeline for REMS
- July 24, 2009 S-028 REMS Amendment

Background:

S-026
Package Insert

NDA 19-591 for Lariam® (mefloquine hydrochloride) Tablets, 250 mg, was originally approved on May 2, 1989. The last approved labeling revision for Lariam® (mefloquine hydrochloride) Tablets, 250 mg (NDA 19-591/S-027) was on June 26, 2009, when revisions to the package insert regarding the use of Lariam® (mefloquine hydrochloride) Tablets, 250 mg in the pediatric population for both malaria treatment and malaria prophylaxis were approved. No additional labeling revisions have been approved since that date.

S-026, submitted on November 19, 2008, proposed revisions to the Medication Guide and to the **CLINICAL PHARMACOLOGY**, **WARNINGS**, **PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the package insert as well as editorial revisions as follows (~~strikethrough~~=deletion, underline=addition):

1. Under the **CLINICAL PHARMACOLOGY**/Pharmacokinetics/Metabolism subsection;

   Metabolism

   Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved. (b) (4)

Two metabolites of mefloquine 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 of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

2. Under the **WARNINGS** section;

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.

(b) (4)

~~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).~~

3. Under the **PRECAUTIONS**/ Central and Peripheral Nervous System Effects subsection;

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 or vertigo, 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. In a small number of patients, dizziness or vertigo (b) (4) and loss of balance have been reported to continue for months after

discontinuation of the drug ~~mefloquine has been stopped~~ (see **ADVERSE REACTIONS: Postmarketing**).

4. Under the **PRECAUTIONS**/Information for Patients subsection;

   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, including dizziness or vertigo and loss of balance, and it may be necessary to change medications. Although side effects of dizziness or vertigo and loss of balance are usually mild and do not cause people to stop taking the medication, in a small number of patients it has been reported that these symptoms may continue for months after discontinuation of the drug;

5. Under the **PRECAUTIONS**/Drug Interactions subsection;

   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: Cardiac Effects**). 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 (b) (4) ~~danger~~ of a potentially fatal prolongation of the QTc interval, halofantrine must not be given (b) (4) ~~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~~.

(b) (4)

(b) (4) Clinically significant QTc prolongation has not been found with mefloquine alone.

(b) (4)

(b) (4)

Mefloquine does not inhibit or induce the (b) (4) P450 enzyme system. (b) (4) (b) (4)

(b) (4)

Substrates and Inhibitors of P-glycoprotein

It has been shown in vitro that mefloquine is a substrate and an inhibitor of P-glycoprotein (b) (4) Therefore, drug-drug interactions could also occur with drugs that are substrates or are known to modify the expression of this transporter. The clinical relevance of these interactions are not known to date.

7. Under the **ADVERSE REACTIONS**/Postmarketing subsection;

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 swings ~~changes~~, panic attacks, memory impairment ~~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 less frequently reported ~~infrequent~~ adverse events include:

Cardiovascular Disorders: circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular heart rate ~~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, hyperhidrosis ~~sweating~~, chills, dyspepsia and loss of appetite

8. Under the **ADVERSE REACTIONS**/Laboratory;

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

9. Under the Revision subsection

   Revised: Month/Year (b) (4)

10. Under the **MEDICATION GUIDE/**In addition subsection;

    - **Be careful driving or in other activities** needing alertness and careful movements (fine motor coordination). Lariam can cause dizziness (b) (4) (b) (4) or loss of balance, even after you stop taking Lariam (see "**What are the possible side effects of Lariam?**").

11. Under the **MEDICATION GUIDE/**What are the possible side effects of Lariam subsection:

    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 or vertigo, loss of balance, difficulty sleeping, and bad dreams. These side effects are usually mild and do not cause people to stop taking the medicine. However, in a small number of patients, it has been reported that dizziness or vertigo and loss of balance may continue for months after stopping Lariam.

12. Medication Guide Revised: Month/Year (b) (4)

13. The Lariam wallet card was revised as follows:

    Card Revised: Month/Year (b) (4)

Revision of the following text from:

Distributed by:

Roche Pharmaceuticals

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

To:

Distributed by:

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

A March 12, 2009, facsimile transmission (FAX) from the Division of Special Pathogen and Transplant Products (DSPTP) requested that the following revisions be made to the labeling submitted by Roche November 19, 2008 in S-026 (~~strikethrough~~=deletion, underline=addition):

1. Under the **WARNINGS** section;

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.

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam d(b)(4)ue to the risk of a potentially fatal prolongation of ~~the~~ QTc interva (b) (4) (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam d(b)(4)ue to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increase(b)(4)s plasma concentrations and elimination half-life of mefloquine following co-administration (b) (4) (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and 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.

2. Under the **PRECAUTIONS/** Drug Interactions subsection;

PRECAUTIONS
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: Cardiac Effects**). 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.

Halofantrine and Other Antimalarials

Halofantrine should not be administered with Lariam or within 15 weeks of the last does of Lariam due to (b) (4) the risk of a potentially fatal prolongation of the QTc interva (b) (4) (see **WARNINGS**).

Concomitant administration of Lariam and other related antimalarial 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.

(b) (4)

Clinically significant QTc prolongation has not been found with mefloquine alone.

Ketoconazole (potent inhibitor of CYP3A4)
Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in a increase in the mean Cmax and AUC of mefloquine by 64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. (see **WARNINGS**)

Other Drugs that Prolong the QTc Interval

~~This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically,~~ (b) (4) Co-administration of other drugs known to alter cardiac conduction (eg, antiarrhythmic 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.

Anticonvulsants

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**).

Vaccines

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.~~

Rifampin (potent inducer of CYP3A4)
Co-administration of a single 500 mg oral dose of Lariam and 600 mg of rifampin once daily for 7 days in 7 healthy Thai volunteers resulted in a decrease in the mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

(b) (4)

Inhibitors and Inducers of CYP3A4
Mefloquine does not inhibit or induce the (b) (4) CYP 450 enzyme system. (b) (4) hus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers (b) (4) may (b) (4) increase or decrease (b) (4) mefloquine plasma concentrations, respectively.

(b) (4)

Substrates and Inhibitors of P-glycoprotein
It has been shown in vitro that mefloquine is a substrate and an inhibitor of P-glycoprotein. Therefore, drug-drug interactions could also occur with drugs that

are substrates or are known to modify the expression of this transporter. The clinical relevance of these interactions (b) (4) is not known to date.
Other Potential Interactions
No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

In an amendment to S-026 dated March 31, 2009, Roche agreed to all the proposed revisions recommended by DSPTP in the March 12, 2009 FAX.

In the March 31, 2009, submission the proposed revisions were as follows:

(~~strikethrough~~=deletion, underline=addition)

1. Under the **CLINICAL PHARMACOLOGY**/Pharmacokinetics/Metabolism subsection;

   Metabolism

   Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved.

   Two metabolites of mefloquine have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive 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 of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

2. Under the **WARNINGS** section;

   Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

   Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following co-administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and PRECAUTIONS: Drug Interactions).

~~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).~~

3. Under the **PRECAUTIONS**/ Central and Peripheral Nervous System Effects subsection;

   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 <u>or vertigo</u>, 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. In a small number of patients, dizziness <u>or vertigo</u> and loss of balance have been reported to continue for months after <u>discontinuation of the drug</u> ~~mefloquine has been stopped~~(see **ADVERSE REACTIONS: Postmarketing**).

4. Under the **PRECAUTIONS**/Information for Patients subsection;

   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, including dizziness <u>or vertigo</u> and loss of balance, and it may be necessary to change medications. Although side effects of dizziness <u>or vertigo</u> and loss of balance are usually mild and do not cause people to stop taking the medication, in a small number of patients it has been reported that these symptoms may continue for months after discontinuation of the drug;

5. Under the **PRECAUTIONS**/ Drug Interactions subsection;

   <u>Halofantrine and Other Antimalarials</u>

   <u>Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to</u> the <u>risk</u> (b) (4) 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 <u>antimalarial</u> 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.

Ketoconazole (Potent Inhibitor of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in an increase in the mean Cmax and AUC of mefloquine by 64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see WARNINGS).

Other Drugs that Prolong the QTc Interval

~~This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically~~ (b) (4) Co-administration 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.

Anticonvulsants

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**).

Vaccines

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.~~

Rifampin (Potent Inducer of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam and 600 mg of rifampin once daily for 7 days in 7 healthy Thai volunteers resulted in a decrease in the

mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

Inhibitors and Inducers of CYP3A4

Mefloquine does not inhibit or induce the CYP 450 enzyme system. Thus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers may increase or decrease mefloquine plasma concentrations, respectively.

Substrates and Inhibitors of P-glycoprotein

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

Other Potential Interactions

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

6. Under the **ADVERSE REACTIONS**/Postmarketing subsection;

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 swings ~~changes~~, panic attacks, memory impairment ~~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 less frequently reported ~~infrequent~~ adverse events include:

Cardiovascular Disorders: circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular

heart rate ~~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, hyperhidrosis ~~sweating~~, chills, dyspepsia and loss of appetite

7. Under the **ADVERSE REACTIONS**/Laboratory;

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

8. Under the Revision subsection;

   Revised: Month/Year (b) (4)

S-026 and S-028

Medication Guide

S-026 Medication Guide (MG) Revisions and S-028 Supplement for Proposed Risk Evaluation and Mitigation Strategy (REMS)

On February 17, 2009, the Division sent a consult to OSE/DRISK to review the proposed Medication Guide. After discussion between the Division and DRISK, it was concluded that the drug interaction between Lariam and ketoconazole is considered a new safety issue, and the sponsor would have to implement an MG only REMS to ensure that an MG is given to each patient receiving the product.

The MG submitted on November 19, 2008 was revamped by DRISK to align the content and format with 21 CFR 208. DRISK completed their review of the MG on April 30, 2009. On May 4, 2009, a FAX was sent to Roche by the Division, informing Roche that the revised MG submitted on November 19, 2008, as part of NDA 19-591/S-026, had been reviewed and additional revisions to the MG were now being proposed. Roche submitted a response to the May 4, 2009, facsimile communication on May 26, 2009, proposing additional revisions to the MG for Lariam® (mefloquine hydrochloride). The Division and DRISK reviewed the May 26, 2009 proposed MG. On June 3, 2009, DDMAC completed review of the MG revised per DRISK review dated April 30, 2009. The Division and DRISK reviewed the comments from DDMAC and all three Divisions agreed upon revisions to the MG. On June 16, 2009, the Division sent another FAX to Roche with revisions to the MG requesting that Roche submit the MG exactly as

presented in the communication. On June 29, 2009, a FAX was sent to Roche requesting the MG be amended to include the updated information from the approval of labeling supplement S-027. On July 29, 2009, the Division sent an email to Roche with additional revisions to the MG. On August 3, 2009, Roche submitted the revised MG with all revisions (June 16, June 29 Faxes and July 29 email) incorporated.

S-028

Risk Evaluation and Mitigation Strategy (REMS)

Roche submitted NDA 19-591/S-028 on May 14, 2009, in response to an April 17, 2009, letter from the Division that informed Roche that a REMS would be necessary for Lariam® (mefloquine hydrochloride) Tablets due to new safety information related to serious adverse events due to a drug interaction between Lariam and ketoconazole.

The Division submitted a consult on June 1, 2009 to OSE/DRISK to review the proposed REMS submission. On June 22, 2009, DRISK completed the review of the REMS submission and the Division sent a FAX to Roche with the revisions to the REMS program on this date. On July 24, 2009, Roche submitted the revised REMS as outlined by the Division.

Electronic Labeling Comparison:

S-026

Package Insert

The content of labeling for the package insert submitted on November 19, 2008, for NDA 19-591/S-026 was electronically compared with the labeling approved on June 26, 2009 for S-027 Lariam® (mefloquine hydrochloride) Tablets, 250 mg. Subsequent to that electronic labeling comparison, the content of revised labeling for the package insert submitted on March 31, 2009, was electronically compared with the June 26, 2009, approved content of labeling for the package insert for Lariam® (mefloquine hydrochloride).

All of the proposed revisions in the March 12, 2009, Revised Proposed Draft Labeling communication for the package insert were included and agreed to by Roche in the March 31, 2009 submission.

The final agreed upon revisions for the package insert for Lariam® (mefloquine hydrochloride) Tablets, 250 mg NDA 19-591/S-026 are, detailed in Roche's March 31, 2009, submission. These revisions have been previously outlined in this review.

Review:

S-026

Package Insert

Dr. Chilukuri's February 27, 2009 Clinical Pharmacology review recommended revisions to the package insert submitted on November 19, 2008 in S-026. These recommendations were included in the FAX to Roche dated March 12, 2009.

In Dr. Chilukuri's July 8, 2009, Clinical Pharmacology review, he agrees with the proposed revisions to the package insert submitted by Roche on March 31, 2009 in response to the FDA's March 12, 2009 FAX.

In her Clinical review dated April 4, 2009, Dr. O'Shaughnessy recommends approval of the proposed revisions in S-026 to the package insert and the addition of the term vertigo to the Medication Guide. Dr. O'Shaughnessy also notes in her April 4, 2009, review that a potential drug-drug interaction between ketoconazole and mefloquine was appropriately added to the Medication Guide by Roche. As new safety information is being added to the Medication Guide, a REMS is required along with a complete review of the Medication Guide by OSE/DRISK. Therefore, Dr. O'Shaughnessy's April 4, 2009, review refers to the August 19, 2009, review regarding REMS, by Dr. Ozlem Belen, Deputy Director for Safety and the Medication Guide Review.

Medication Guide and REMS

Please refer to Dr. Ozlem Belen's Medication Guide review dated August 19, 2009. Please also refer to DRISK review of the MG dated April 30, 2009 and REMS review dated June 22, 2009. Please also refer to DDMAC review of the MG dated June 3, 2009.

Conclusions/Recommendations:

S-026

Package Insert

In summary, NDA 19-591/S-026 submitted by Hoffman La Roche on November 19, 2008, proposed revisions to the product labeling to include revisions to the **CLINICAL PHARMACOLOGY**, **WARNINGS**, **PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the package insert as well as editorial revisions. In addition, Roche proposed revisions to the **Medication Guide** for Lariam® (mefloquine hydrochloride) Tablets, 250 mg to update information regarding a ketoconazole drug interaction, CYP3A4 metabolism, mefloquine metabolism, and the addition of vertigo as an adverse event.

Dr. Chilukuri's reviews dated February 27, 2009 and July 8, 2009 and Dr. O'Shaughnessy's review dated April 4, 2009, both recommend approval of S-026.

We recommend that this supplemental application be approved and an approval letter should issue.

Medication Guide

Under FDAAA, Medication Guides are required in accordance with 21 CFR 208. DRISK and DDMAC revised the MG accordingly and with the Division's agreement provided revisions to Roche. Roche submitted the MG in agreement with the Division's revisions. As the MG is part of the Package Insert, we recommend that the MG be approved and that an approval letter issue.

S-028

Risk Evaluation and Mitigation Strategy (REMS)

The new safety information required that Roche implement a REMS program to ensure that an MG is given to each patient receiving the product. DRISK and the Division reviewed and revised the REMS and Roche agreed to all revisions suggested by the Division. We recommend that the MG only REMS be approved and that an approval letter issue.

Gregory DiBernardo
Regulatory Project Manager

Hyun Son, Pharm.D.
Acting 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/

GREGORY F DIBERNARDO
08/19/2009
Please Review and Complete Signing

HYUN J SON
08/20/2009

DIANA M WILLARD
08/20/2009
Project Management Review of NDA 19-591/S-026 and S-028

DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS (DSPTP)

Lariam (Mefloquine) Medication Guide and Information Wallet Review

NDA: 19-591/S-026
19-591/S-028

Submission Date(s): November 19, 2008 (S-026)
May 14, 2009 (S-028)

Applicant: Hoffmann-La Roche Inc.

Review Date: August 17, 2009

DRISK Consultant: Robin Duer, RN, MBA

DDMAC Consultant: Sharon Watson, PharmD

I. Background and summary:
Since Lariam® (mefloquine hydrochloride) was approved on May 2, 1989, we have become aware of a serious risk resulting from an interaction between Lariam® (mefloquine hydrochloride) and ketoconazole, based on our review of peer-reviewed medical literature. [1] Ketoconazole increases plasma concentration and elimination half-life of Lariam® (mefloquine hydrochloride) following co-administration. The risk of potentially fatal prolongation of QTc is increased if ketoconazole is taken during Lariam® (mefloquine hydrochloride) therapy for prophylaxis or treatment of malaria, or within 15 weeks after the last dose of Lariam® (mefloquine hydrochloride) due to the long half life of Lariam® (mefloquine hydrochloride). This information was not available when Lariam® (mefloquine hydrochloride) was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

In addition, this information was to be added to the existing Medication Guide (MG) which required revisions to the MG.. In accordance with section 505-1 of the FDCA, as one element of Risk Evaluation and Mitigation Strategy (REMS), FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Lariam® (mefloquine hydrochloride) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Lariam® (mefloquine hydrochloride). FDA has determined that Lariam® is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Lariam® (mefloquine hydrochloride). FDA has also determined that Lariam®

[1] Ridtitid K. et al. Ketoconazole increases plasma concentrations of antimalarial mefloquine in healthy volunteers. J Clin Pharm Ther 2005; 30:285-90.

(mefloquine hydrochloride) is a product for which patient labeling could help prevent serious adverse events.
In response to the April 17, 2009 letter (requesting revisions to the MG and submission of REMS), the applicant submitted prior approval labeling supplement to include the proposed Medication Guide (MG) and REMS on May 14, 2009. The Sponsor sent agreed upon wording for the Medication Guide and the Information Wallet Card on July 2, 2009 and August 3, 2009 and the labeling on March 31, 2009.

NDA 19-591/S-026 submitted by Hoffman La Roche on November 19, 2008, proposed revisions to the product labeling to include revisions to the **CLINICAL PHARMACOLOGY**, **WARNINGS**, **PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the package insert as well as editorial revisions. In addition, Roche proposed revisions to the **Medication Guide** for Lariam® (mefloquine hydrochloride) Tablets, 250 mg to update information regarding a ketoconazole drug interaction, CYP3A4 metabolism, mefloquine metabolism, and the addition of vertigo as an adverse event.

Dr. Chilukuri's reviews dated February 27, 2009 and July 8, 2009 and
Dr. O'Shaughnessy's review dated April 4, 2009, both recommend approval of S-026.

In an amendment to S-026 dated March 31, 2009, Roche agreed to all the proposed revisions recommended by DSPTP.

In the March 31, 2009, submission the proposed revisions were as follows:

(~~strikethrough~~=deletion, underline=addition)

1. Under the **CLINICAL PHARMACOLOGY**/Pharmacokinetics/Metabolism subsection

   Metabolism

   Mefloquine is extensively metabolized in the liver by the cytochrome P450 system. In vitro and in vivo studies strongly suggested that CYP3A4 is the major isoform involved.

   Two metabolites of mefloquine have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive 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 of the metabolite, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3 to 5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

2. Under the **WARNINGS** section

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increases plasma concentrations and elimination half-life of mefloquine following co-administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and PRECAUTIONS: Drug Interactions).

~~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).~~

3. ***Under the*** *PRECAUTIONS/* ***Central and Peripheral Nervous System Effects subsection:***

   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 or vertigo, 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. In a small number of patients, dizziness or vertigo and loss of balance have been reported to continue for months after discontinuation of the drug ~~mefloquine has been stopped~~(see **ADVERSE REACTIONS: Postmarketing**).

4. Under the **PRECAUTIONS**/Information for Patients subsection

   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, including dizziness or vertigo and loss of balance, and it may be necessary to change medications. Although side effects of dizziness or vertigo and loss of balance are usually mild and do not cause people to stop taking the medication, in a small number of patients it has been reported that these symptoms may continue for months after discontinuation of the drug;

5. Under the **PRECAUTIONS**/ Drug Interactions subsection

Halofantrine and Other Antimalarials

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk (b) (4) 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 antimalarial 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.

Ketoconazole (Potent Inhibitor of CYP3A4)

Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in an increase in the mean Cmax and AUC of mefloquine by 64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval (see WARNINGS).

Other Drugs that Prolong the QTc Interval

~~This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically, c~~ (b) (4) Co-administration 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.

Anticonvulsants

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**).

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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.~~

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mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

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Mefloquine does not inhibit or induce the CYP 450 enzyme system. Thus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers may increase or decrease mefloquine plasma concentrations, respectively.

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

Other Potential Interactions

No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

6. Under the **ADVERSE REACTIONS**/Postmarketing subsection

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 swings ~~changes~~, panic attacks, memory impairment ~~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 less frequently reported ~~infrequent~~ adverse events include:

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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, hyperhidrosis ~~sweating~~, chills, dyspepsia and loss of appetite

7. Under the **ADVERSE REACTIONS**/Laboratory

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

8. Under the Revision subsection

   Revised: Month/Year (b) (4)

II. Materials Reviewed

1. DDMAC Review by Sharon Watson, PharmD dated 6/3/2009.
2. DRISK review by Robin Duer, RN, MBA dated 4/29/2009
3. Sponsor submission dated August 3, 2009 which includes the proposed Medication Guide
4. Lariam prescribing Information (PI), Medication Guide (MG), Information Wallet Card approved on 6/26/09
5. DRISK Consult Review of REMS May 14, 2009 Submission (dated June 22, 2009)

III. Review of the Medication Guide

The full Medication Guide is attached as an Appendix at the end of this review.

1. The sponsor will provide phonetic spelling and the dosage form in the heading section of the Medication Guide (MG).

2. Under "What is the most important information I should know about Lariam?" we revised the bullet. We think it is better to keep the word "paranoia" than not, even though it is medical, for many people are familiar with it, the definition was left in the document. DRISK reviewed agreed vial e-mail.
    - paranoia (feelings of mistrust towards others)

3. (b) (4) keep the statement, "ask your healthcare provider or pharmacist for a list of these medicines if you are not sure." This was done under "What should I tell my doctor before taking Lariam?"

4. The following is a separate bullet and includes list of tradenames for Rifampin and Rifampin containing products:

    "Rifampin and Rifampin containing products (Rifadin, Rifamate, Rifater, Rimactane) used to treat infections"

5. Under "How should I take Lariam?", (b) (4) the Review Division left this section as it was. DRISK team was notified.

6. (b) (4) The following bullet was modified with concurrence from the DRISK team under "What are the possible side effects of Lariam?"

    - "dizziness or loss of balance (vertigo)"

7. The following wording was deleted since the MG went under overall review and is comprehensive. It is not only intended for travelers who are taking Lariam to prevent malaria but all patients who take it.

    "**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"**

    In addition, the following wording was added into the box, as per guidance received from DRISK:

"**Your doctor or pharmacist will give you an Information Wallet Card along with this Medication Guide.**"

8. The word "rarely" was taken out of the following sentence, since it does not reflect the current labeling. DRISK agreed with this deletion.

   "**Lariam can ~~rarely~~ cause serious mental problems.** "

9. Under "**What is the most important information I should know about Lariam?**" and "**Lariam can cause serious mental problems.** " the following bullet was added as per DDMAC and DRISK guidance. This is in line with the WARNINGS section of the PI.

   - feeling restless

10. Under "**What is the most important information I should know about Lariam?**" and " In some patient these serious side effect can go on after Lariam is stopped." the word "suicide" was defined (putting an end to their life) as DRISK reviewer explained that patient labeling is written for a 6th to 8th grade comprehension level. (b) (4) The section will read as follows:

    - Some people who take Lariam think about suicide (putting an end to their life). Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

11. DDMAC reviewer commented that the instruction to take Lariam "after you return from a malaria area" lacks important context from the **DOSAGE AND ADMINISTRATION** section of the proposed PI, that "prophylaxis must be continued **for 4 additional weeks** to ensure suppressive blood levels of the drug when merozoites emerge from the liver." DRISK reviewer agreed with this assessment, and therefore this information was added to the MG as follows:

    "If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine for another 4 weeks."

12. DRISK reviewer disagreed with the DDMAC comment about moving the three statements, beginning with "You need to take malaria prevention…" to "How should I take Lariam?" section as this is critical information for the patient to know. These statements are listed in the PI under Precautions, so are appropriately placed in the "What is the most important information I should know about Lariam?" section. The DSPTP reviewer agrees with the DRISK comment

regarding this DDMAC suggestion.

13. DSPTP reviewer agrees with the DRISK and DDMAC comment about adding the word concept of "fatal" to the sentence below; and incorporated that these heart problems "can lead to death" as per DRISK suggestion.

- Do not take halofantrine (used to treat malaria) or ketoconazole (used for fungal infections) with Lariam or within 15 weeks of your last dose of Lariam. You may have serious heart problems that can lead to death. Do not take quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat) with Lariam. You may have serious heart problems.

14. DRISK reviewer disagreed with DDMAC's comment about adding more specific microbiology information concerning different strains of malaria in this section. Patient labeling is written for a 6^{th} to 8^{th} grade reading comprehension level and microbiology information is too technical for a patient to understand. DSPTP reviewer agrees with this assessment. Therefore DSPTP proposed Lariam does not work for all types of malaria" under "What is Lariam?" section; both DRISK and DDMAC reviewers agreed to this via e-mail.

15. DRISK and DDMAC reviewers commented about adding information that women of childbearing potential should also be advised to practice contraception during malaria prophylaxis with Lariam and for up to 3 months thereafter, and that malaria chemoprophylaxis is not considered an indication for pregnancy termination. However, the statement proposed by DDMAC was found too technical and comprehensive for a patient to understand. Therefore the following wording will be included in line with the current PI:

"Use birth control while you take Lariam and for 3 months after you stop Lariam. If you have an unplanned pregnancy, talk to your doctor right away."

16. DRISK reviewer agreed with DDMAC's comment about adding a statement advising the patient to see a doctor for a fever that occurs after return from a malaria area, and to tell the doctor that they may have been exposed to malaria and the following wording was added:

"After leaving a malaria area, if you have a fever contact your doctor right away."

17. The Review Division agrees with the DRISK reviewer about adding specific dosing information for pediatric patients. Specific dosing instructions are not included, as the doctor will determine the best dosing for the patient. We agree that a statement should be added about the treatment of pediatric patients under 6 months, and it will say in line with the current PI:

"It is not known if Lariam is safe and effective in children under 6 months old for the treatment of malaria."

In addition, the following wording was also added under the same section to reflect the June 26, 2009 approved labeling revisions for Lariam:

It is not known how well Lariam works to prevent malaria in infants weighing less than 44 lbs (20kg).

Jody Duckhorn of the DRISK team was notified via e-mail on June 29, 2009 and proposed the patient friendly language above.

18. DSPTP reviewer agrees with DRISK and DDMAC comment about changing the liver function statement to read "liver function to see if there has been damage to your liver".

19. DSPTP agrees with DRISK reviewer (and DDMAC comment) about adding "for months" to the following sentence under "**What should I avoid while taking Lariam**?":

"Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you. You may feel dizzy or lose your balance. This could happen for months after you stop taking Lariam."

20. The most common side effects for both treatment vs. prophylaxis were listed. The most common side effects that were observed specifically in patients who take Lariam for treatment were listed under a separate group in line with the current PI.

21. DDMAC recommended including information on vomiting which may be common in pediatric patients and has been cited as a possible cause of treatment failure. The DDMAC reviewer recommended including a statement to make the patients aware of this risk. The following text was proposed under "How should I take Lariam?" DRISK and DDMAC reviewers agreed.

"If you vomit after taking Lariam, call your healthcare provider to see if you should take another dose"

22. In an e-mail dated June 16, 2009, the sponsor proposed to add "feeling restless to the appropriate section in the Information Wallet Card for consistency. DSPTP agreed.
The term "muscle pain" was left in the listing of the most common side effects of Lariam (b) (4)

IV. Conclusion

The Medication Guide has been revised to incorporate additional safety information included in labeling and is located at the end of the Package Insert.

The review of the Medication Guide in this supplemental application, NDA 19-591/S-026 as amended, is completed. The Medical Reviewer recommends that this supplemental application can be approved.

Appendix

MEDICATION GUIDE

Lariam (LAH-ree-am)

(mefloquine hydrochloride)
Tablets

Read this entire Medication Guide before you start taking Lariam and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

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

Your doctor or pharmacist will give you an Information Wallet Card along with this Medication Guide. It has important information about Lariam and should be carried with you at all times while you take Lariam.

Lariam can cause serious mental problems.

- Some people who take Lariam have sudden serious mental problems, including:
  - severe anxiety
  - paranoia (feelings of mistrust towards others)
  - hallucinations (seeing or hearing things that are not there)
  - depression
  - feeling restless
  - unusual behavior
  - feeling confused

In some patients these serious side effects can go on after Lariam is stopped.

- Some people who take Lariam think about suicide (putting an end to their life). Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

  If you have any of these serious mental problems, or you develop other serious side effects or mental problems, you should call your doctor right

away as it may be necessary to stop taking Lariam and use another medicine to prevent malaria.

You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area. If you are told by a doctor to stop taking Lariam because of the side effects or for other reasons, you will need to take another malaria medicine.

If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine for another 4 weeks.

- Do not take halofantrine (used to treat malaria) or ketoconazole (used for fungal infections) with Lariam or within 15 weeks of your last dose of Lariam. You may have serious heart problems that can lead to death. Do not take quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat) with Lariam. You may have serious heart problems.
- Do not take quinine (Qualaquin) or chloroquine (Aralen) (used to treat malaria) with Lariam. You may have a greater risk for convulsions (seizures).

What is Lariam?

Lariam is a prescription medicine used to prevent and treat malaria. Malaria can be a life-threatening infection. Lariam does not work for all types of malaria.

It is not known if Lariam is safe and effective in children under 6 months old for the treatment of malaria.

It is not known how well Lariam works to prevent malaria in infants weighing less than 44 lbs (20 kg).

Who should not take Lariam?

Do not take Lariam if you have:
- depression or had depression recently
- had recent mental problems, including anxiety disorder, schizophrenia, or psychosis (losing touch with reality)
- seizures or had seizures (epilepsy or convulsions)
- an allergy to quinine, quinidine, Lariam or any ingredients in Lariam. See the end of this Medication Guide for a complete list of ingredients in Lariam.

Talk to your doctor before you take Lariam if you have any of the conditions listed above.

What should I tell my doctor before taking Lariam?

Before taking Lariam, tell your doctor about all your medical conditions, including if you have:

- heart disease
- liver problems
- seizures or epilepsy
- diabetes
- blood clotting problems or take blood thinner medicines (anticoagulants)
- mental problems
- are pregnant or plan to become pregnant. It is not known if Lariam will harm your unborn baby. Talk to you doctor if you are pregnant or plan to become pregnant.
- use birth control while you take Lariam and for 3 months after you stop Lariam. If you have an unplanned pregnancy, talk to your doctor right away.
- are breast-feeding or plan to breast-feed. Lariam can pass through your milk and may harm your baby. Ask your doctor whether you will need to stop breast-feeding or use another medicine.

After leaving a malaria area, if you have a fever contact your doctor right away.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lariam and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Especially tell your doctor if you take:

- ketoconazole used to treat fungal infections
- halofantrine, quinine (Qualaquin), quinidine, chloroquine (Aralen) or other medicines used to treat malaria
- anti-arrhythmic medicines, beta-adrenergic blocking medicines and calcium channel blockers used to treat heart problems or high blood pressure
- antihistamines or H_1-blocking agents used to treat allergies
- tricyclic antidepressants used to treat depression
- phenothiazines used to treat mental problems
- anticonvulsants used to treat seizures
- vaccines containing live bacteria. Your doctor may want you to finish receiving your vaccines at least 3 days before you start Lariam.
- rifampin and rifampin-containing products (Rifadin, Rifamate, Rifater, Rimactane) used to treat infections

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

How should I take Lariam?

- Take Lariam exactly as your doctor tells you to take it. Your doctor will tell you how many Lariam to take and when to take them.

- You will start taking Lariam to prevent malaria between 1 to 3 weeks before you travel to a malaria area.
- Take Lariam just after eating your main meal and with at least one cup (8 ounces) of water.
- Do not take Lariam on an empty stomach.
- If you vomit after taking Lariam, call your healthcare provider to see if you should take another dose.
- Continue taking Lariam for 4 weeks after returning from a malaria area**.**
- Lariam tablets may be crushed and mixed with a small amount of water, milk or other beverage for children or other people unable to swallow Lariam whole. Your doctor will tell you the correct dose for your child based on your child's weight.
- If you take Lariam for a year or longer, your doctor should check your
    - eyes, especially if you have trouble seeing while you take Lariam
    - liver function to see if there has been damage to your liver
- Use protective clothing, insect repellents, and bednets to protect you from being bitten by mosquitoes. Medicine alone does not always stop you from catching malaria from mosquito bites.

What should I avoid while taking Lariam?

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you. You may feel dizzy or lose your balance. This could happen for months after you stop taking Lariam. See "What are the possible side effects of Lariam?"

What are the possible side effects of Lariam?

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

Lariam may cause serious side effects, including:
- convulsions (seizures)
- liver problems
- heart problems

The most common side effects of Lariam include:
- nausea
- vomiting
- diarrhea
- abdominal pain
- dizziness or loss of balance (vertigo), which may continue for months after Lariam is stopped
- headache
- sleeping problems (sleepiness, unable to sleep, bad dreams)

The most common side effects in people who take Lariam for treatment include:
- muscle pain

- fever
- chills
- skin rash
- fatigue
- loss of appetite
- ringing in the ears
- irregular heart beat

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lariam. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lariam?

- Store Lariam between 59ºF to 86ºF (15ºC to 30ºC)
- Safely throw away medicine that is out of date or no longer needed.

Keep Lariam and all medicines out of the reach of children.

General information about the safe and effective use of Lariam.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lariam for a condition for which it was not prescribed. Do not give Lariam to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Lariam. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lariam that is written for health professionals.

If you have any questions or would like more information about Lariam, you can call Roche, the manufacturer of Lariam, at 1-800-526-6367.

What are the ingredients in Lariam?

Active ingredients: mefloquine hydrochloride

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

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

Reprint of information wallet card:

Information Wallet Card

Lariam® (mefloquine hydrochloride) Tablets

It is important that you read the entire Medication Guide for additional information on Lariam.

Carry this 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.

Lariam can cause serious mental problems in some people. If you take Lariam and you have sudden signs of serious mental problems (such as: severe anxiety, feelings of mistrust towards others, seeing or hearing things that are not there, depression, feeling restless, unusual behavior or feeling confused), you should contact a doctor right away as it may be necessary to stop taking Lariam and take different medicine to prevent malaria.

Other side effects from Lariam may include: convulsions, liver problems, and heart problems. The most common side effects of Lariam include nausea, vomiting, diarrhea, abdominal pain, dizziness or loss of balance (vertigo) which may continue for months after Lariam is stopped, headache, and sleeping problems (sleepiness, unable to sleep, bad dreams).

While you take Lariam, do not take:

- **Halofantrine (used to treat malaria)**
- **Ketoconazole (used for fungal infections)**
- **Quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat)**
- **Chloroquine (Aralen) (used to treat malaria)**

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you.

Other medicines are approved in the United States for malaria prevention. However, not all malaria medicines work equally well in different malaria areas. Before you travel, talk to your doctor about your travel plans.

If you have any serious side effects, and cannot get another medicine, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

Card Revised: Month/Year

Manufactured by:

F. HOFFMANN-LA ROCHE LTD
Basel, Switzerland

Distributed by:

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

Revised: Month/Year

LMT_215998_MG_MMYYYY_N

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 19591	SUPPL 26		LARIAM
NDA 19591	SUPPL 26		LARIAM
NDA 19591	SUPPL 26		LARIAM
NDA 19591	SUPPL 26		LARIAM
NDA 19591	SUPPL 26		LARIAM
NDA 19591	SUPPL 28		LARIAM
NDA 19591	SUPPL 28		LARIAM
NDA 19591	SUPPL 28		LARIAM
NDA 19591	SUPPL 28		LARIAM

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/s/

OZLEM A BELEN
08/19/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 29, 2009
To:	Renata Albrecht, M.D., Director **Division of Special Pathogen and Transplant Products**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Robin Duer, RN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling, Medication Guide, Information Wallet Card
Drug Name(s):	Lariam® (mefloquine hydrochloride) Tablets
Application Type/Number:	NDA 19-591
Submission Number:	026
Applicant/sponsor:	Roche Laboratories, Inc.
OSE RCM #:	2009-569

1 INTRODUCTION

On November 19, 2008 the Agency received a prior approval labeling supplement (S-026) from Roche Laboratories, Inc., which provided for revised labeling in the Prescribing Information (PI), Medication Guide (MG) and Information Wallet Card for Lariam. The proposed labeling was based on new information learned regarding

- Ketoconazole drug interaction
- CYP3A4 metabolism
- Mefloquine metabolism
- Adverse events for vertigo after discontinuation of Lariam
- New MedDRA terms for adverse events
- Editorial changes

Following review of the November 19, 2008 submission, the Division of Special Pathogen and Transplant Products (DSPTP) requested that Roche make additional revisions to the Lariam labeling as faxed to Roche on March 12, 2009. Roche submitted revised labeling to the Agency as DSPTP requested on March 31, 2009.

On March 27, 2009 the DSPTP requested that the Division of Risk Management (DRISK) review the March 12, 2009 version of the proposed Lariam patient labeling, and completely overhaul the Medication Guide.

2 MATERIALS REVIEWED

- Lariam Medication Guide (MG) version dated March 12, 2009
- Lariam Prescribing Information (PI) version dated March 12, 2009
- Lariam Information Wallet Card version dated March 12, 2009

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the Applicant and revised by DSPTP has a Flesch Kinkaid grade level of 10.5, and a Flesch Reading Ease score of 46.3. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 7.9 and a Flesch Reading Ease score of 59.9%. In our current review of the MG and Information Wallet Card we

- simplified the wording and clarified concepts where possible
- ensured that the MG and Information Wallet Card are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
- revised the information wallet card so that the most important information from the MG appears there

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We recommend reformatting the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG and Information Wallet Card. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG and Information Wallet Card. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG and Information Wallet Card.

4 CONCLUSIONS AND RECOMMENDATIONS

- We added section headers consistent with 21CFR 208, including, "What is Lariam?", "What should I tell my doctor before taking Lariam?", How should I store Lariam?", and "What are the ingredients in Lariam?"
- The applicant should provide the phonetic spelling of Lariam where indicated.
- The terms "doctor", "prescriber" and "health care provider" were used by the applicant interchangeably throughout the MG. One term should be used for consistency and easier readability. We used the term "doctor".
- A small box was added to the beginning of the Medication Guide to let the patient know about the importance of the attached wallet card.
- In the "What is the most important information I should know about Lariam?" section
    - We moved the bullet that discusses "serious mental problems" to the first bullet because it is the most important information. We deleted the term" rarely" or "rare" as it minimizes this serious adverse event.
    - We deleted the disease specific information concerning malaria. The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. Preferably information about malaria should be addressed with the patient separately from the product specific information.
    - We deleted the bullet that includes information about taking Lariam exactly as prescribed. We added that information to the new second bullet because "taking Lariam exactly as prescribed" does not necessarily need to be a stand-alone bullet.
    - We added three new bullets concerning warnings about drug interactions because serious and significant risk information should be prominently placed. This section

typically includes all pertinent patient information from Boxed or Bolded Warnings in the PI.

- In the "How should I take Lariam?" section

(b) (4)

  - We added more specific dosing instructions for children and people unable to swallow whole tablets from the PI as that information was not complete.
  - We added common side effects in patient-friendly language as listed in the PI. We deleted the term "vertigo" as the definition is "loss of balance and dizziness", both of which are already listed under side effects. Revise the serious and most common side effects list as necessary.

- In the "General information about the safe and effective use of Lariam" section, the applicant should add information on how to reach the manufacturer by telephone or website.
- We moved the location of the Lariam manufacturer information from after the wallet card to the end of the Medication Guide as the wallet card is an attachment that will be removed from the document.
- For the Information Wallet Card we
  - revised the information to reflect our changes to the Medication Guide
  - included the most important information from the Medication Guide that the patient should know while traveling

Please let us know if you have any questions.

15 Pages Draft Labeling have been Withheld in Full as B4 (TS/CCI) Immediately Following this Page

MEDICATION GUIDE

Lariam *[DRISK Comment: Applicant should provide phonetic spelling here]*

(mefloquine hydrochloride)

Read this Medication Guide before you start taking Lariam and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

[DRISK Comment: use this small box to prominently place certain

(b) (4) **It has important information about Lariam and should be carried with you at all times while you take Lariam.**

important information.]

(b) (4)

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

- **Lariam can cause serious mental problems.** Some people who take Lariam have sudden serious mental problems, including:
  - severe anxiety

(b) (4)

  - hallucinations (seeing or hearing things that are not there)
  - depression
  - unusual behavior
  - feeling confused

(b) (4)

  - Some people who take Lariam think about suicide (b) (4) Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

If you have any of these serious mental problems, you should stop taking Lariam and call your doctor right away. Your doctor will give you another medicine to prevent malaria.

[DRISK Comment: Since the adverse event of "serious mental problems" is the most important information this bullet should be listed

first. (b) (4)

[DRISK Comment: The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. This disease specific information can be placed at the end of the Medication Guide after the "Ingredients" section or preferably be addressed with the patient separately from the product specific information.]

[DRISK Comment: This information does not warrant its own bullet and has been included under the second bullet.]

- 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.

  (b) (4)

  If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area. (b) (4)

- Do not take Halofantrine (used to treat malaria) or Ketoconazole (used for fungal infections) with Lariam or within 15 weeks of your last dose of Lariam. You may have serious heart problems.

(b) (4)

[DRISK Comment: Serious and significant risk information should be prominently placed. This section should include patient pertinent information from Boxed or Bolded Warnings in the PI.]

What is Lariam?

Lariam is a prescription medicine used to prevent and treat malaria. Malaria can be a life-threatening infection.

Who should not take Lariam?

Do not take Lariam if you have:

- depression or had depression recently
- had recent mental problems, including anxiety disorder, schizophrenia, or psychosis (losing touch with reality)
- seizures or had seizures (epilepsy or convulsions)
- an allergy to quinine or quinidine. See the end of this leaflet for a complete list of ingredients in Lariam.

Talk to your doctor before you take Lariam if you have any of the conditions listed above.

What should I tell my doctor before taking Lariam?

Before Taking Lariam, tell your doctor about all your medical conditions, including if you have:

- heart disease
- liver problems
- seizures or epilepsy
- diabetes
- blood clotting problems or take blood thinner medicines (anticoagulants)
- mental problems
- are pregnant or plan to become pregnant. It is not known if Lariam will harm your unborn baby. Talk to you doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. Lariam can pass through your milk and may harm your baby. Therefore, ask your doctor whether you will need to stop breast-feeding or use another medicine.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lariam and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Especially tell your doctor if you take:

- Ketoconazole used to treat fungal infections
- Halofantrine, quinine (Qualaquin), quinidine , chloroquine (Aralen) or other medicines used to treat malaria

- Anti-arrhythmic medicines, beta-adrenergic blocking medicines and calcium channel blockers used to treat heart problems or high blood pressure
- Anticonvulsants used to treat seizures
- Vaccines containing live bacteria. Your doctor may want you to finish receiving your vaccines at least 3 days before you start Lariam.
- Rifampin (Rifadin) used to treat infections

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

(b) (4)

How should I take Lariam?

- Take Lariam exactly as your doctor tells you to take it. Your doctor will tell you how many Lariam to take and when to take them.
- You will start taking Lariam between 1 to 3 weeks before you travel to a malaria area.
- (b) (4)
- Continue taking Lariam for four weeks after returning from a malaria area。
- Lariam tablets may be crushed and mixed with a small amount of water, milk or other beverage. (b) (4) Your doctor will tell you the correct dose for your child based on your child's weight. ***[DRISK Comment: We added more specific dosing instructions for children and people unable to swallow whole tablets from the PI*** (b) (4)
- If you take Lariam for a year or longer, your doctor should check your
    - eyes, especially if you have trouble seeing while you take Lariam
    - liver function to make sure there is no damage to your liver
- Use protective clothing, insect repellents, and bednets to protect you from being bitten by mosquitoes. Medicine alone does not always stop you from catching malaria from mosquito bites.

What should I avoid while taking Lariam?

Avoid activities such a driving a car or using heavy machinery until you know how Lariam affects you. You may feel dizzy or lose your balance, even after you stop taking Lariam. See "What are the possible side effects of Lariam?"

What are the possible side effects of Lariam?

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

Lariam may cause serious side effects, including

- convulsions (seizures)
- liver problems
- heart problems

The most common side effects of Lariam include nausea and vomiting

- diarrhea
- abdominal pain
- dizziness
- loss of balance
- muscle pain
- headache
- sleeping problems (sleepiness, unable to sleep, bad dreams)
- fever
- chills
- skin rash
- fatigue
- loss of appetite
- ringing in your ears
- irregular heart beat

[DRISK Comment: We added common side effects in patient-friendly language as listed in the PI. (b) (4)

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lariam. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lariam?

- Store Lariam between 59ºF to 86ºF (15ºC to 30ºC)
- Safely throw away medicine that is out of date or no longer needed.

Keep Lariam and all medicines out of the reach of children.

General information about the safe and effective use of Lariam.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lariam for a condition for which it was not prescribed. Do not give Lariam to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Lariam. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lariam that is written for health professionals.

[DRISK Comment: Include information here on how to reach the manufacturer by telephone or web site.]

What are the ingredients in Lariam?

Active ingredients: mefloquine hydrochloride
Inactive ingredients: ammonium-calcium alginate, corn starch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer #331, and talc.

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

Distributed by:

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

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

(b) (4) Month/Year

Reprint of information wallet card:

Information Wallet Card

Lariam® (mefloquine hydrochloride) Tablets

It is important that you read the Medication Guide for additional information on Lariam.

Carry this 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.

Lariam can cause serious mental problems. If you take Lariam and you have sudden signs of serious mental problems (such as: severe anxiety, (b) (4) seeing or hearing things that are not there, depression, unusual behavior or feeling confused), (b) (4) contact a doctor right away. (b) (4) take different medicine to prevent malaria.

Other side effects from Lariam include: convulsions, liver problems, heart problems, nausea and vomiting, diarrhea, abdominal pain, dizziness, loss of balance, (b) (4) (b) (4)

While you take Lariam, do not take:

- **Halofantrine (used to treat malaria),**
- **Ketoconazole (used for fungal infections),**
- **quinine (Qualaquin) or quinidine (used to treat malaria)**
- **chloroquine (Aralen) (used to treat malaria)**

Avoid activities such as driving a car or using heaving machinery until you know how Lariam affects you.

(b) (4) If you have any serious side effect, and can not get another medicine, leave the malaria area. (b) (4)

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

[DRISK Comment: The wallet card was revised to include the most important information about Lariam and reflect our revisions in the Medication Guide.]

[DRISK Comment: The manufacturer information was moved to the end of the Medication Guide since the wallet card is an attachment that will be removed from the rest of the document.]

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

/s/

Robin E Duer
4/30/2009 03:43:39 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/30/2009 03:54:03 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-026&028

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Dear Ms. DeVenezia-Tobias,

We refer to your May 26, 2009, submission to NDA 19-591/S-026 where you submitted revisions to the Medication Guide and the FDA facsimile communication dated, June 16, 2009 where FDA proposed final edits to the Medication Guide for Lariam.

FDA is now requesting that an additional revision be made to the June 16, 2009, version of the Medication Guide. This revision will update the Medication Guide to reflect the June 26, 2009, approved labeling revisions for Lariam.

Please make the revision to the Medication Guide exactly as outlined below and submit the updated Medication Guide to the NDA no later than July 8, 2009.

FDA Requested Revision to Lariam Medication Guide:
(Additions = underline and Deletions = strikethrough)

1. **Under the What is Lariam? section of the Medication Guide**

   What is Lariam?

   Lariam is a prescription medicine used to prevent and treat malaria. Malaria can be a life-threatening infection. Lariam does not work for all types of malaria.

   It is not known if Lariam is safe and effective in children under 6 months old for the treatment of malaria.

   It is not known how well Lariam works to prevent malaria in infants weighing less than 44 lbs (20 kg).

If you have any questions regarding this transmittal, please contact me at (301) 796-4063.

Sincerely,

Gregory F. DiBernardo
Regulatory Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Gregory F DiBernardo
6/29/2009 04:44:25 PM
CSO
S-026 Updated Medication Guide Revision

Please refer to your May 26, 2009 submission. We have reviewed the Medication Guide (MG) for Lariam and have attached the revised the MG. Please submit the MG (exactly as attached).

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Acting Safety Regulatory Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

MEDICATION GUIDE
Lariam **(LAH-ree-am)**
(mefloquine hydrochloride)
Tablets

Read this entire Medication Guide before you start taking Lariam and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

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

Your doctor or pharmacist will give you an Information Wallet Card along with this Medication Guide. It has important information about Lariam and should be carried with you at all times while you take Lariam.

Lariam can cause serious mental problems.

- Some people who take Lariam have sudden serious mental problems, including:
  - severe anxiety
  - paranoia (feelings of mistrust towards others)
  - hallucinations (seeing or hearing things that are not there)
  - depression
  - feeling restless
  - unusual behavior
  - feeling confused

In some patients these serious side effects can go on after Lariam is stopped.

- Some people who take Lariam think about suicide (putting an end to their life). Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

If you have any of these serious mental problems, or you develop other serious side effects or mental problems, you should call your doctor right away as it may be necessary to stop taking Lariam and use another medicine to prevent malaria.

You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area. If you are told by a doctor to stop taking Lariam because of the side effects or for other reasons, you will need to take another malaria medicine.

If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine for another 4 weeks.

- Do not take halofantrine (used to treat malaria) or ketoconazole (used for fungal infections) with Lariam or within 15 weeks of your last dose of Lariam. You may have serious heart problems that can lead to death. Do not take quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat) with Lariam. You may have serious heart problems.
- Do not take quinine (Qualaquin) or chloroquine (Aralen) (used to treat malaria) with Lariam. You may have a greater risk for convulsions (seizures).

What is Lariam?

Lariam is a prescription medicine used to prevent and treat malaria. Malaria can be a life-threatening infection. Lariam does not work for all types of malaria.

It is not known if Lariam is safe and effective in children under 6 months old for the treatment of malaria.

Who should not take Lariam?

Do not take Lariam if you have:

- depression or had depression recently
- had recent mental problems, including anxiety disorder, schizophrenia, or psychosis (losing touch with reality)
- seizures or had seizures (epilepsy or convulsions)
- an allergy to quinine, quinidine, Lariam or any ingredients in Lariam. See the end of this Medication Guide for a complete list of ingredients in Lariam.

Talk to your doctor before you take Lariam if you have any of the conditions listed above.

What should I tell my doctor before taking Lariam?

Before taking Lariam, tell your doctor about all your medical conditions, including if you have:

- heart disease
- liver problems
- seizures or epilepsy
- diabetes
- blood clotting problems or take blood thinner medicines (anticoagulants)
- mental problems

- are pregnant or plan to become pregnant. It is not known if Lariam will harm your unborn baby. Talk to you doctor if you are pregnant or plan to become pregnant.
- Use birth control while you take Lariam and for 3 months after you stop
- Lariam. If you have an unplanned pregnancy, talk to your doctor right
- away.

- are breast-feeding or plan to breast-feed. Lariam can pass through your milk and may harm your baby. (b) (4) ask your doctor whether you will need to stop breast-feeding or use another medicine.

After leaving a malaria area, if you have a fever contact your doctor right away.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lariam and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Especially tell your doctor if you take:
- ketoconazole used to treat fungal infections
- halofantrine, quinine (Qualaquin), quinidine , chloroquine (Aralen) or other medicines used to treat malaria
- anti-arrhythmic medicines, beta-adrenergic blocking medicines and calcium channel blockers used to treat heart problems or high blood pressure
- antihistamines or H_1-blocking agents used to treat allergies
- tricyclic antidepressants used to treat depression
- phenothiazines used to treat mental problems
- anticonvulsants used to treat seizures
- vaccines containing live bacteria. Your doctor may want you to finish receiving your vaccines at least 3 days before you start Lariam.
- rifampin and rifampin containing products (Rifadin, Rifamate, Rifater, Rimactane) used to treat infections

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

How should I take Lariam?

- Take Lariam exactly as your doctor tells you to take it. Your doctor will tell you how many Lariam to take and when to take them.
- You will start taking Lariam to prevent malaria between 1 to 3 weeks before you travel to a malaria area.
- Take Lariam just after eating your main meal and with at least one cup (8 ounces) of water.
- Do not take Lariam on an empty stomach.

- If you vomit after taking Lariam, call your healthcare provider to see if you should take another dose.
- Continue taking Lariam for four weeks after returning from a malaria area**.**
- Lariam tablets may be crushed and mixed with a small amount of water, milk or other beverage for children or other people unable to swallow Lariam whole. Your doctor will tell you the correct dose for your child based on your child's weight.

- If you take Lariam for a year or longer, your doctor should check your
    - eyes, especially if you have trouble seeing while you take Lariam
    - liver function to see if there has been damage to your liver

- Use protective clothing, insect repellents, and bednets to protect you from being bitten by mosquitoes. Medicine alone does not always stop you from catching malaria from mosquito bites.

What should I avoid while taking Lariam?

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you. You may feel dizzy or lose your balance. This could happen for months after you stop taking Lariam. See "What are the possible side effects of Lariam?"

What are the possible side effects of Lariam?

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

Lariam may cause serious side effects, including:

- convulsions (seizures)
- liver problems
- heart problems

The most common side effects of Lariam include

- nausea
- vomiting
- diarrhea
- abdominal pain
- dizziness or loss of balance (vertigo), which may continue for months after Lariam is stopped
- headache
- sleeping problems (sleepiness, unable to sleep, bad dreams)

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

- fever
- chills

- skin rash
- fatigue
- loss of appetite
- ringing in the ears
- irregular heart beat

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lariam. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lariam?

- Store Lariam between 59ºF to 86ºF (15ºC to 30ºC)
- Safely throw away medicine that is out of date or no longer needed.

Keep Lariam and all medicines out of the reach of children.

General information about the safe and effective use of Lariam.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lariam for a condition for which it was not prescribed. Do not give Lariam to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Lariam. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lariam that is written for health professionals.

If you have any questions or would like more information about Lariam, you can call Roche, the manufacturer of Lariam, at 1-800-526-6367.

What are the ingredients in Lariam?

Active ingredients: mefloquine hydrochloride
Inactive ingredients: ammonium-calcium alginate, corn starch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer #331, and talc.

Manufactured by:

F. HOFFMANN-LA ROCHE LTD
Basel, Switzerland

Distributed by:

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

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

(b) (4)

Reprint of information wallet card:

Information Wallet Card

Lariam® (mefloquine hydrochloride) Tablets
It is important that you read the entire Medication Guide for additional information on Lariam.
Carry this 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.

Lariam can cause serious mental problems in some people. If you take Lariam and you have sudden signs of serious mental problems (such as: severe anxiety, feelings of mistrust towards others, seeing or hearing things that are not there, depression, unusual behavior or feeling confused), you should contact a doctor right away as it may be necessary to stop taking Lariam and take different medicine to prevent malaria.

Other side effects from Lariam may include: convulsions, liver problems, and heart problems. The most common side effects of Lariam include nausea, vomiting, diarrhea, abdominal pain, dizziness or loss of balance (vertigo) which may continue for months after Lariam is stopped, headache, and sleeping problems (sleepiness, unable to sleep, bad dreams).

While you take Lariam, do not take:

- **Halofantrine (used to treat malaria),**
- **Ketoconazole (used for fungal infections),**
- **Quinine (Qualaquin) or quinidine (used to treat malaria or irregular heart beat)**
- **Chloroquine (Aralen) (used to treat malaria)**

Avoid activities such as driving a car or using heavy machinery or other activities needing alertness and careful movements (fine motor coordination) until you know how Lariam affects you.

Other medicines are approved in the United States for malaria prevention. However, not all malaria medicines work equally well in different malaria areas. Before you travel, talk to your doctor about your travel plans.

If you have any serious side effects, and cannot get another medicine, leave the malaria area and contact a doctor as soon as possible because leaving the malaria area may not protect you from getting malaria. You will still need to take a malaria prevention medicine.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

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

/s/

Hyun Son
6/16/2009 11:34:29 AM
CSO

Please refer to your November 19, 2008 submission. We have reviewed the Medication Guide (MG) for Lariam and have revised the MG as attached. Please address the comments in brackets [ ] in the MG (3 comments).

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Hyun Son, Pharm. D.
Acting Safety Regulatory Project Manager
Division of Special Pathogen and Transplant Products
FDA/CDER/OND/OAP

MEDICATION GUIDE

Lariam ***[Provide phonetic spelling here]***
(mefloquine hydrochloride)

Read this Medication Guide before you start taking Lariam and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

[Use this small box to prominently place certain important information.]

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

(b) (4) **It has important information about Lariam and should be carried with you at all times while you take Lariam.**

- **Lariam can cause serious mental problems.** Some people who take Lariam have sudden serious mental problems, including:
  - severe anxiety
  - paranoia (feelings that people are against them)
  - hallucinations (seeing or hearing things that are not there)
  - depression
  - unusual behavior
  - feeling confused

These serious side effects can go on months after Lariam is stopped.

- Some people who take Lariam think about suicide (b) (4) Some people who were taking Lariam committed suicide. It is not known whether Lariam was responsible for those suicides.

If you have any of these serious mental problems, (b) (4)

- **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 you are told by a doctor to stop taking Lariam because of the side effects or for other reasons, you will need to take another malaria medicine.

  If you do not have access to a doctor or to another medicine and have to stop taking Lariam, leave the malaria area. (b) (4)

- (b) (4)

- Do not take quinine (Qualaquin) or quinidine (used to treat malaria) with Lariam. You may have serious heart problems.
- Do not take quinine (Qualaquin) or chloroquine (Aralen) (used to treat malaria) with Lariam. You may have a greater risk for convulsions (seizures).

What is Lariam?

(b) (4)

Who should not take Lariam?

Do not take Lariam if you have:

- depression or had depression recently
- had recent mental problems, including anxiety disorder, schizophrenia, or psychosis (losing touch with reality)
- seizures or had seizures (epilepsy or convulsions)
- (b) (4)

Talk to your doctor before you take Lariam if you have any of the conditions listed above.

What should I tell my doctor before taking Lariam?

Before Taking Lariam, tell your doctor about all your medical conditions, including if you have:

- heart disease
- liver problems
- seizures or epilepsy
- diabetes
- blood clotting problems or take blood thinner medicines (anticoagulants)
- mental problems
- are pregnant or plan to become pregnant. It is not known if Lariam will harm your unborn baby. Talk to you doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. Lariam can pass through your milk and may harm your baby. Therefore, ask your doctor whether you will need to stop breast-feeding or use another medicine.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Lariam and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

Especially tell your doctor if you take:

- Ketoconazole used to treat fungal infections

- Halofantrine, quinine (Qualaquin), quinidine , chloroquine (Aralen) or other medicines used to treat malaria
- Anti-arrhythmic medicines, beta-adrenergic blocking medicines and calcium channel blockers used to treat heart problems or high blood pressure
- Anticonvulsants used to treat seizures
- Vaccines containing live bacteria. Your doctor may want you to finish receiving your vaccines at least 3 days before you start Lariam.
- Rifampin and Rifampin containing products (Rifadin, Rifamate, Rifater, Rimactane) used to treat infections

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

How should I take Lariam?

- Take Lariam exactly as your doctor tells you to take it. Your doctor will tell you how many Lariam to take and when to take them.
- You will start taking Lariam between 1 to 3 weeks before you travel to a malaria area.
- (b) (4)
- Continue taking Lariam for four weeks after returning from a malaria area.
- (b) (4)
- If you take Lariam for a year or longer, your doctor should check your
  - eyes, especially if you have trouble seeing while you take Lariam
  - liver function to make sure there is no damage to your liver
- Use protective clothing, insect repellents, and bednets to protect you from being bitten by mosquitoes. Medicine alone does not always stop you from catching malaria from mosquito bites.

What should I avoid while taking Lariam?

Avoid activities such a driving a car or using heavy machinery until you know how Lariam affects you. You may feel dizzy or lose your balance, (b) (4) . See "What are the possible side effects of Lariam?"

What are the possible side effects of Lariam?

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

Lariam may cause serious side effects, including

- convulsions (seizures)
- liver problems
- heart problems

The most common side effects of Lariam include nausea and vomiting

- diarrhea
- abdominal pain
- dizziness or loss of balance (vertigo)

(b) (4)

- headache
- sleeping problems (sleepiness, unable to sleep, bad dreams)

(b) (4)

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Lariam. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lariam?

- Store Lariam between 59ºF to 86ºF (15ºC to 30ºC)
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General information about the safe and effective use of Lariam.

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This Medication Guide summarizes the most important information about Lariam. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Lariam that is written for health professionals.

[Include information here on how to reach the manufacturer by telephone or web site.]

What are the ingredients in Lariam?

Active ingredients: mefloquine hydrochloride
Inactive ingredients: ammonium-calcium alginate, corn starch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer #331, and talc.

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

Distributed by:

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Nutley, New Jersey 07110-1199

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

(b) (4)

Reprint of information wallet card:

Information Wallet Card

Lariam® (mefloquine hydrochloride) Tablets

It is important that you read the Medication Guide for additional information on Lariam.
Carry this 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.

Lariam can cause serious mental problems. If you take Lariam and you have sudden signs of serious mental problems (such as: severe anxiety, (b) (4) seeing or hearing things that are not there, depression, unusual behavior or feeling confused), stop taking Lariam and contact a doctor right away. You may need to take different medicine to prevent malaria.

Other side effects from Lariam include: convulsions, liver problems, heart problems, (b) (4)

While you take Lariam, do not take:

- **Halofantrine (used to treat malaria),**
- **Ketoconazole (used for fungal infections),**
- **quinine (Qualaquin) or quinidine (used to treat malaria)**
- **chloroquine (Aralen) (used to treat malaria)**

Avoid activities such as driving a car or using heaving machinery until you know how Lariam affects you.

(b) (4) If you have any serious side effect, and can not get another medicine, leave the malaria area. Leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

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

/s/

Hyun Son
5/4/2009 04:05:35 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
DDMAC
Paul Loebach

FROM: Division of Special Pathogen and Transplant Products
Hyun Son, Pharm.D., Acting Safety Project Manager
301-796-1939

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 1, 2009		19-591/S-026	SLR	November 19, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lariam (mefloquine hydrochloride)	Standard	Antimalarial	May 15, 2009

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: Please review the proposed Medguide for Lariam. The MedGuide was reviewed by DRISK (review in the eRoom). Because this drug interaction will be included in the label as a new safety information, we have requested the sponsor to submit a MG only REMS for this product. Once the REMS is submitted, we'll forward that to you as well. Please let me know if you need access to the eRoom. Thank you.
http://eroom.fda.gov/eRoom/CDER/CDER-DSPIDPL/0_8e58c

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Hyun Son, Pharm.D.	☐e-mail ■ DFS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Hyun Son

5/1/2009 12:34:23 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Office of Surviellence and Epidemiology
DRISK

FROM: Division of Special Pathogen and Transplant Products
Hyun Son, Pharm.D., Acting Safety Project Manager
301-796-1939

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 27, 2009		19-591/S-026	SLR	November 19, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lariam (mefloquine hydrochloride)	Standard	Antimalarial	April 30, 2009

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
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- ☐ 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: Please review the proposed PI and the proposed Medguide for Lariam. The MedGuide will need to be revised as a whole (MedGuide included with PI before FDAAA was initiated). Because this drug interaction will be included in the label as a new safety information, we will be requesting the sponsor to submit a MG only REMS for this product. Once the REMS is submitted, we'll forward that to you as well. I have placed the proposed PI and the proposed MedGuide in the eRoom link below. Please let me know if you need access to the eRoom. Thank you.
http://eroom.fda.gov/eRoom/CDER/CDER-DSPIDPL/0_8be9e

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Hyun Son, Pharm.D.	☐e-mail ■ DFS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Hyun Son

3/27/2009 02:38:50 PM

Dear Ms. DeVenezia-Tobias,

In order to assist in the review of your November 19, 2008 submission, Prior Approval Supplement 026, to NDA 19-591 please review the following comments from the Division of Special Pathogen and Transplant Products (DSPTP). We have reviewed your submitted product label changes and are now proposing additional revisions to your November 19, 2008 submission. At this point in time DSPTP would like to place emphasis on only the sections of the product label listed below.

If you agree with the proposed product label changes please submit these proposed changes officially to NDA 19-591 as a labeling amendment to your November 19, 2008 submission, including a complete product label in Structured Product Label (SPL) format.

In addition, please provide a clean version of the entire amended product label and a marked up version of the amended product label as two MS word documents. Please provide these documents to me via e-mail attachment as soon as they are available, in addition to submitting these documents officially to the NDA.

DSPTP Proposed Changes to Lariam Label:

FDA changes are given as double underline = additions; or ~~strikethroughs~~ = deletions

1. WARNINGS

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.

Halofantrine should not be administered with Lariam or within 15 weeks of the last dose of Lariam d(b)(4)ue to the risk of a potentially fatal prolongation of ~~the~~ QTc interval(b)(4) (b) (4) (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination).

Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam d(b)(4)ue to the risk of a potentially fatal prolongation of the QTc interval. Ketoconazole increase(b)(4)s plasma concentrations and elimination half-life of mefloquine following co–administration (b) (4) (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elimination and 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.

2. PRECAUTIONS, Drug Interactions

PRECAUTIONS
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: Cardiac Effects**). 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.

Halofantrine and Other Antimalarials
Halofantrine should not be administered with Lariam or within 15 weeks of the last does of Lariam due to ~~Because of~~ the risk of a potentially fatal prolongation of the QTc interval~~,~~ ~~halofantrine~~ (b) (4) (see **WARNINGS**).

Concomitant administration of Lariam and other related antimalarial 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.

(b) (4)

Clinically significant QTc prolongation has not been found with mefloquine alone.

Ketoconazole (potent inhibitor of CYP3A4)
Co-administration of a single 500 mg oral dose of Lariam with 400 mg of ketoconazole once daily for 10 days in 8 healthy volunteers resulted in a increase in the mean Cmax and AUC of mefloquine by 64% and 79%, respectively, and an increase in the mean elimination half-life of mefloquine from 322 hours to 448 hours. Ketoconazole should not be administered with Lariam or within 15 weeks of the last dose of Lariam due to the risk of a potentially fatal prolongation of the QTc interval. (see **WARNINGS**)

Other Drugs that Prolong the QTc Interval

~~This appears to be the only clinically relevant interaction of this kind with Lariam, although theoretically,~~ (b) (4) Co-administration 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.

Anticonvulsants

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**).

Vaccines

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.~~

Rifampin (potent inducer of CYP3A4)
Co-administration of a single 500 mg oral dose of Lariam and 600 mg of rifampin once daily for 7 days in 7 healthy Thai volunteers resulted in a decrease in the mean Cmax and AUC of mefloquine by 19% and 68%, respectively, and a decrease in the mean elimination half-life of mefloquine from 305 hours to 113 hours. Rifampin should be used cautiously in patients taking Lariam.

~~**Other Potential Interactions**~~

Inhibitors and Inducers of CYP3A4
Mefloquine does not inhibit or induce the (b) (4)-CYP 450 enzyme system. (b) (4) (b) (4)

Thus, concomitant administration of Lariam and substrates of the CYP 450 enzyme system is not expected to result in a drug interaction. However, co-administration of CYP 450 inhibitors or inducers (b) (4) may (b) (4) increase or decrease (b) (4) mefloquine plasma concentrations, respectively.

(b) (4)

Substrates and Inhibitors of P-glycoprotein
It has been shown in vitro that mefloquine is a substrate and an inhibitor of P-glycoprotein. Therefore, drug-drug interactions could also occur with drugs that are substrates or are known to modify the expression of this transporter. The clinical relevance of these interactions (b) (4) is not known to date.

Other Potential Interactions
No other drug interactions are known. Nevertheless, the effects of Lariam on travelers receiving co-medication, 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 of mefloquine.

If you have any questions regarding this transmittal, please contact me at (301) 796-1600.

Sincerely,

Gregory F. DiBernardo
Regulatory Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Gregory F DiBernardo
3/12/2009 01:22:35 PM
CSO
Proposed Labeling Changes to November 19, 2008 Prior Approval Supplement 026

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Office of Surviellence and Epidemiology
DRISK

FROM: Division of Special Pathogen and Transplant Products
Hyun Son, Pharm.D., Acting Safety Project Manager
301-796-1939

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 17, 2009		19-591/S-026	SLR	November 19, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lariam (mefloquine hydrochloride)	Standard	Antimalarial	February 27, 2009

NAME OF FIRM: Roche

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- ☐ CLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS: Please review the labeling supplement for Lariam which incorporates the word “vertigo” into the PI and the medication guide of the product. This is not a FDAAA related labeling change and there is no REMS for this product. DSPTP Medical reviewer is in agreement with the proposed sponsor labeling.
Below is the link to the submission. Please forward any questions to me or Ozlem Belen. Thank you.
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Hyun Son, Pharm.D.	☐e-mail ■ DFS ☐ HAND
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/s/

Hyun Son
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-026 **PRIOR APPROVAL SUPPLEMENT**

Hoffmann-La Roche Inc.
Attention: Ms. Lynn DeVenezia-Tobias
Senior Program Manager, Diversified Products
340 Kingsland Street
Nutley, NJ 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: 026

Date of supplement: November 19, 2008

Date of receipt: November 20, 2008

This supplemental application proposes revisions to the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert and in the Medication Guide for Lariam® (mefloquine hydrochloride) to update information regarding a ketoconazole drug interaction, CYP3A4 metabolism, mefloquine metabolism, addition of an adverse event (vertigo) reported after discontinuation of Lariam, and editorial revisions.

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 Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Diana Willard
12/15/2008 05:42:54 PM
NDA 19-591/S-026 Acknowledgement