CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 019591/S-027

Trade Name:	Lariam for oral use, 250mg
Generic or Proper Name:	Mefloquine Hydrochloride
Sponsor:	Hoffman-LaRoche, Inc.
Approval Date:	June 26, 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-027
CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-027

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

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug application (sNDA) dated April 23, 2009, received April 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

This supplemental new drug application (sNDA) provides for revisions to the Lariam® labeling to update the **DOSAGE AND ADMINSTRATION**/Pediatric Patients and **DOSAGE AND ADMINISTRATION**/Pediatric Patients/Malaria Prophylaxis subsections to include information that reflects text supported by current data.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. This application provides for the following revisions to the content of labeling for the package insert (additions are noted with underline and deletions are noted with ~~strikethrough~~):

1. Under the **DOSAGE AND ADMINISTRATION**/Pediatric Patients subsection:

   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 ~~infants less than 3 months old or~~ weighing less than 20~~5~~ kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

2. Under the **DOSAGE AND ADMINISTRATION**/Pediatric Patients/Malaria Prophylaxis subsection:

   Malaria Prophylaxis

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

   30 to 45 kg: 3/4 tablet
   20 to 30 kg: 1/2 tablet
   ~~10 to 20 kg: 1/4 tablet~~
   ~~5 to 10 kg: 1/8 tablet~~~~*~~

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

   Experience with Lariam in pediatric patients ~~infants less than 3 months old or~~ weighing less than 20 ~~5~~ kg is limited.

   Revised: Month/Year ~~September 2008~~

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling (text for the package insert). 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-027**."

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in 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.

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).

(b) (4) Please submit an amendment to that supplement to update the text of the labeling to include the revisions approved in this supplement.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-027

LABELING

LARIAM®

brand of

mefloquine hydrochloride

TABLETS

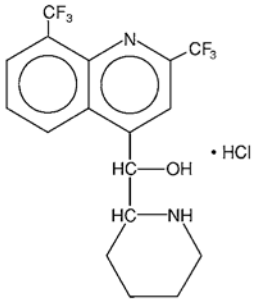
R_X only

DESCRIPTION

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

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

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



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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an intravenous formulation is not available. The bioavailability of the tablet formation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. In healthy volunteers, plasma concentrations peak 6 to 24 hours (median, about 17 hours) after a single dose of Lariam. In a similar group of volunteers, maximum plasma concentrations in μg/L are

roughly equivalent to the dose in milligrams (for example, a single 1000 mg dose produces a maximum concentration of about 1000 μg/L). In healthy volunteers, a dose of 250 mg once weekly produces maximum steady-state plasma concentrations of 1000 to 2000 μg/L, which are reached after 7 to 10 weeks.

Distribution

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

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

Metabolism

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

Elimination

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

Pharmacokinetics in Special Clinical Situations

Children and the Elderly

No relevant age-related changes have been observed in the pharmacokinetics of mefloquine. Therefore, the dosage for children has been extrapolated from the recommended adult dose.

No pharmacokinetic studies have been performed in patients with renal insufficiency since only a small proportion of the drug is eliminated renally. Mefloquine and its main metabolite are not appreciably removed by hemodialysis. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy persons.

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

The pharmacokinetics of mefloquine may be altered in acute malaria.

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

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

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

Microbiology

Mechanism of Action

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

Activity In Vitro and In Vivo

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

Drug Resistance

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

Cross-Resistance

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

LARIAM® (mefloquine hydrochloride)

INDICATIONS AND USAGE

Treatment of Acute Malaria Infections

Lariam is indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible strains of *P. falciparum* (both chloroquine-susceptible and resistant strains) or by *Plasmodium vivax.* There are insufficient clinical data to document the effect of mefloquine in malaria caused by *P. ovale* or *P. malariae.*

> *Note:* Patients with acute *P. vivax* malaria, treated with Lariam, are at high risk of relapse because Lariam does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse, after initial treatment of the acute infection with Lariam, patients should subsequently be treated with an 8-aminoquinoline derivative (eg, primaquine).

Prevention of Malaria

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

CONTRAINDICATIONS

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

WARNINGS

In case of life-threatening, serious or overwhelming malaria infections due to *P. falciparum,* patients should be treated with an intravenous antimalarial drug. Following completion of intravenous treatment, Lariam may be given to complete the course of therapy.

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

Mefloquine may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior. On occasions, these symptoms have been reported to continue long after mefloquine has been stopped. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed. To minimize the chances of these adverse events, mefloquine should not be taken for prophylaxis in patients with active depression or with a recent history of depression,

generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders. Lariam should be used with caution in patients with a previous history of depression.

During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.

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

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

PRECAUTIONS

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, 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 and loss of balance have been reported to continue for months after mefloquine has been stopped (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 and loss of balance, and it may be necessary to change medications. Although side effects of dizziness 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.

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

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

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

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

When Lariam is taken concurrently with oral live typhoid vaccines, attenuation of immunization cannot be excluded. Vaccinations with attenuated live bacteria should therefore be completed at least 3 days before the first dose of Lariam.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

Pregnancy

Teratogenic Effects

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

in the case of unplanned pregnancy, malaria chemoprophylaxis with Lariam is not considered an indication for pregnancy termination.

Nursing Mothers

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

Pediatric Use

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

In several studies, the administration of Lariam for the treatment of malaria was associated with early vomiting in pediatric patients. Early vomiting was cited in some reports as a possible cause of treatment failure. If a second dose is not tolerated, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use

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

ADVERSE REACTIONS

Clinical

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

Among subjects who received mefloquine for prophylaxis of malaria, the most frequently observed adverse experience was vomiting (3%). Dizziness,

syncope, extrasystoles and other complaints affecting less than 1% were also reported.

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

Two serious adverse reactions were cardiopulmonary arrest in one patient shortly after ingesting a single prophylactic dose of mefloquine while concomitantly using propranolol (see **PRECAUTIONS: Drug Interactions**), and encephalopathy of unknown etiology during prophylactic mefloquine administration. The relationship of encephalopathy to drug administration could not be clearly established.

Postmarketing

Postmarketing surveillance indicates that the same kind of adverse experiences are reported during prophylaxis, as well as acute treatment. 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 changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, psychotic or paranoid reactions and encephalopathy. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed.

Other infrequent adverse events include:

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

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

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

Respiratory Disorders: dyspnea, pneumonitis of possible allergic etiology

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

Laboratory

The most frequently observed laboratory alterations which could be possibly attributable to drug administration were decreased hematocrit, transient elevation of transaminases, leukopenia and thrombocytopenia. These alterations were observed in patients with acute malaria who received treatment doses of the drug and were attributed to the disease itself.

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

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

OVERDOSAGE

Symptoms and Signs

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

Treatment

Patients should be managed by symptomatic and supportive care following Lariam overdose. There are no specific antidotes. Monitor cardiac function (if possible by ECG) and neuropsychiatric status for at least 24 hours. Provide symptomatic and intensive supportive treatment as required, particularly for cardiovascular disturbances.

DOSAGE AND ADMINISTRATION (see INDICATIONS AND USAGE)

Adult Patients

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

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

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

> *Note:* Patients with acute *P. vivax* malaria, treated with Lariam, are at high risk of relapse because Lariam does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse after initial treatment of the acute infection with Lariam, patients should subsequently be treated with an 8-aminoquinoline derivative (eg, primaquine).

Malaria Prophylaxis

One 250 mg Lariam tablet once weekly.

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

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

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

Pediatric Patients

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

Twenty (20) to 25 mg/kg body weight. Splitting the total therapeutic dose into 2 doses taken 6 to 8 hours apart may reduce the occurrence or severity of adverse effects. Experience with Lariam in 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

LARIAM® (mefloquine hydrochloride)

MEDICATION GUIDE

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

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

This Medication Guide was revised in September 2008. Please read it before you start taking Lariam and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your prescriber (doctor or other health care provider) about Lariam and malaria prevention. Only you and your prescriber can decide if Lariam is right for you. If you cannot take Lariam, you may be able to take a different medicine to prevent malaria.

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

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

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

3. **You need to take malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area.**
   Medicines approved in the United States for malaria prevention include Lariam, doxycycline, atovaquone/proguanil, hydroxychloroquine, and chloroquine. Not all of these drugs work equally as well in all areas of the world where there is malaria. The chloroquines, for example, do not work in areas where the malaria parasite has developed resistance to chloroquine. Lariam may be effective against malaria that is resistant to

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

Who should not take Lariam?

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

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

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

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

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

LARIAM® (mefloquine hydrochloride)

How should I take Lariam?

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

To prevent malaria

- For adults and pediatric patients weighing over 45 kg, take 1 tablet of Lariam at least 1 week before you travel to a malaria area (or 2 to 3 weeks before you travel to a malaria area, if instructed by your prescriber). This starts the prevention and also helps you see how Lariam affects you and the other medicines you take. **Take 1 Lariam tablet once a week**, on the same day each week, while in a malaria area.
- **Continue taking Lariam for 4 weeks after returning from a malaria area.** If you cannot continue taking Lariam due to side effects or for other reasons, contact your prescriber.
- Take Lariam just after a meal and with at least 1 cup (8 ounces) of water.
- For children, Lariam can be given with water or crushed and mixed with water or sugar water. The prescriber will tell you the correct dose for children based on the child's weight.
- If you are told by a doctor or other health care provider to stop taking Lariam due to side effects or for other reasons, it will be necessary to take another malaria medicine. You must take **malaria prevention medicine before you travel to a malaria area, while you are in a malaria area, and after you return from a malaria area. If you don't have access to a doctor or other health care provider or to another medicine besides Lariam and have to stop taking it, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.**

What should I avoid while taking Lariam?

- **Halofantrine (marketed under various brand names)**, a medicine used to treat malaria. Taking both of these medicines together can cause serious heart problems that can cause death.
- **Do not become pregnant.** Women should use effective birth control while taking Lariam.
- **Quinine, quinidine, or chloroquine (other medicines used to treat malaria).** Taking these medicines with Lariam could cause changes in your heart rate or increase the risk of seizures.

In addition:

- **Be careful driving or in other activities** needing alertness and careful movements (fine motor coordination). Lariam can cause dizziness or loss

of balance, even after you stop taking 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, 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 and loss of balance may continue for months after stopping Lariam.

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

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

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

What else should I know about preventing malaria?

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

  Malaria can cause confusion, coma, and seizures. It can cause kidney failure, breathing problems, and severe damage to red blood cells.

However, malaria can be easily diagnosed with a blood test, and if caught in time, can be effectively treated.

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

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

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

General information about the safe and effective use of Lariam.

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

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

Medication Guide Revised: September 2008

Reprint of information wallet card:

Lariam® (mefloquine hydrochloride) **Tablets**

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

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

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

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

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

Please read the Medication Guide for additional information on Lariam.

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

Card Revised: September 2008

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

Distributed by:

Roche Pharmaceuticals

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019591/S-027

CLINICAL REVIEW(S)

Medical Officer Review of Applicant Response to Prior Approval Supplement Request Letter for Lariam (Mefloquine HCl)

Sponsor:	Hoffmann-La Roche Inc. Roche Pharmaceuticals
NDA	19-591/SLR-027
Drug Name:	Mefloquine HCl (Lariam®) 250 mg Tablets
Indication (s):	(b) (4) [redacted]
Medical Officer:	Tafadzwa Vargas-Kasambira, MD, MPH
Acting Team Leader:	Joette Meyer, PharmD
Type of Submission:	Response to FDA's Request for Revision of Dosing Recommendations for Malaria Prophylaxis in Pediatric Patients
Materials Reviewed:	Submission from Hoffmann-La Roche, June 12, 2008; Medical Officer Review, January 15, 2009; Applicant Response to Prior Approval Supplement Request letter, April 23, 2009
Date Review Completed:	May 20, 2009

On April 23, 2009, the applicant submitted a response to the Agency's Prior Approval Supplement Request letter dated March 4, 2009. The Letter had requested that the applicant amend the Pediatric Patients/Malaria Prophylaxis subsection in the DOSAGE AND ADMINISTRATION section of the currently approved package insert to remove the dosing recommendations for pediatric patients less than 20 kg in body weight.

(b) (4)

- The current package insert provides the treating physician with information regarding the dosing of this specific group of patients, and describes how the dosing recommendations were extrapolated from the recommended adult dose.

(b) (4)

(b) (4) the applicant agrees to make the revisions as requested and this submission contains the revised package insert.

Reviewer's Comment: The applicant's revisions are the same as those in the March 4, 2009 supplement request letter and therefore are acceptable.

Finally, of note, the applicant states that manufacture of Lariam tablets 250 mg has been discontinued, and that there are no plans to implement this revised package insert in commercial production.

Reviewer's Comment: The change in the package insert is still important to implement, however, as the generic drug will still be available commercially. Physicians who prescribe the generic drug will have access to the revised package insert and the information that it contains on dosing in pediatric patients.

Recommendation: The Lariam package insert should be revised as stated in the FDA's March 4, 2009 supplement request letter to remove pediatric prophylactic dosing recommendations for children less than 20 kg. The applicant's revised version submitted on April 23, 2009 is acceptable. An approval letter should be sent to the Applicant.

The agreed upon changes to the Pediatric Patients/Malaria Prophylaxis subsection of the Lariam package insert under DOSAGE AND ADMINISTRATION are noted below (addition = double underline; deletion = ~~strikeout~~):

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~~infants less than 3 months old or~~ weighing less than 20~~5~~ kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

Malaria Prophylaxis

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

30 to 45 kg: 3/4 tablet

20 to 30 kg: 1/2 tablet

~~10 to 20 kg: 1/4 tablet~~

~~5 to 10 kg: 1/8 tablet*~~

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

Experience with Lariam in pediatric patients~~infants less than 3 months old or~~ weighing less than 20~~5~~ kg is limited.

Revised: Month/Year~~September 2008~~

Tafadzwa Vargas-Kasambira, MD, MPH
MO, CDER/OND/OAP/DSPTP

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

/s/

Tafadzwa Vargas-Kasambira
5/21/2009 10:04:10 AM
MEDICAL OFFICER

Joette Meyer
5/21/2009 11:22:40 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-027

OTHER REVIEW(S)

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

NDA #	Supplement #	Name of Drug Product	Date of Supplement	Date of Receipt
19-591	S-027	Lariam® (mefloquine hydrochloride) Tablets, 250 mg	April 23, 2009	April 24, 2009

Applicant: Hoffmann-La Roche Inc.

Date of Review: June 2, 2009

Documents Reviewed:

- January 14, 2008 teleconference minutes for NDA 19-591 (Attachment 1)
- June 12, 2008, submission to NDA 19-591 that addressed Action Item # 2 from the January 14, 2008, Teleconference Minutes
- Most recent labeling (text for the package insert) approved on September 23, 2008 (NDA 19-591/S-024 and NDA 19-591/S-025)
- January 15, 2009 Clinical Review of the June 12, 2008 submission
- March 4, 2009, DSPTP Supplement Request Letter to NDA 19-591
- The original proposed SLR application for NDA 19-591/S-027 dated April 23, 2009
- May 11, 2009 Acknowledgement letter for S-027
- May 21, 2009 Clinical Review of S-027

Background:

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 occurred on September 23, 2008, for S-024 and S-025. S-024 provided for the addition of the statement "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." in the section "**What are the possible side effects of Lariam?**" in the Medication Guide, in accordance with the interim final rule "Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products" published in the Federal Register on January 3, 2008. S-025 provided for revisions to the **PRECAUTIONS/**General, **PRECAUTIONS/** Information for Patients, and **ADVERSE REACTIONS/**Postmarketing subsections of the product label. No additional labeling revisions have been approved since that date.

During a January 14, 2008, teleconference between Hoffmann-La Roche (Roche) and Division of Special Pathogen and Transplant Products (DSPTP), Roche agreed to confirm what data are available to support the labeling of malarial prophylaxis in pediatric patients and to update DSPTP within three months. Specifically, the DSPTP stated that to support a claim in the labeling, either clinical data or pharmacokinetic extrapolation

from adult data is required to support the following statement in the **DOSAGE AND ADMINISTRATION/Pediatric Patients**/Malaria Prophylaxis subsection: "Neither the pharmacokinetics, nor the clinical efficacy of these doses have been determined in children owing to the difficulty of acquiring this information in pediatric subjects."

In a submission dated June 12, 2008, Roche provided their justification for the use of Lariam for malaria prophylaxis in pediatric patients and for continued inclusion of this indication in the **DOSAGE AND ADMINISTRATION/Pediatric Patients**/Malaria Prophylaxis subsection of the labeling. Although the June 12, 2008, submission provided sufficient data to retain the pediatric prophylaxis indication and dosing recommendations for patients above 20 kg in body weight, it did not provide sufficient data to support dosing recommendations for pediatric patients less than 20 kg in body weight. Dr. Vargas-Kasimbara states the following in his January 15, 2009, Clinical review of the June 12, 2008 submission, "Given the paucity of data on the safety, pharmacokinetics and efficacy of mefloquine hydrochloride prophylaxis in pediatric patients, it is reasonable to restrict the dosage recommendations in the Pediatric Patients/Malaria Prophylaxis subsection of the Lariam label under **DOSAGE AND ADMINISTRATION** to the weight of the subjects studied in the Weiss publication (i.e., 20 kg and over)."

Based on Dr. Vargas-Kasimbara's January 15, 2009, review, DSPTP sent Roche a Prior Approval Supplement Request letter on March 4, 2009, requesting the following revisions be made to the Lariam® (mefloquine hydrochloride) **DOSAGE AND ADMINISTRATION**/Pediatric Patients/Malaria Prophylaxis subsection of the package insert. (~~strikethrough~~ = deletion, <u>underline</u> = addition)

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

30 to 45 kg: 3/4 tablet
20 to 30 kg: 1/2 tablet
~~10 to 20 kg: 1/4 tablet~~
~~5 to 10 kg: 1/8 tablet1~~

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

Experience with Lariam in <u>pediatric patients</u> ~~infants less than 3 months old or~~ weighing less than ~~5 kg~~ <u>20 kg</u> is limited.

On April 23, 2009, Roche, submitted a prior approval labeling supplement, NDA 19-591/S-027. In addition to the revisions requested to the **DOSAGE AND ADMINISTRATION**/Pediatric Patients/Malaria Prophylaxis subsection of the package insert in the March 4, 2009 Prior Approval Supplement Request Letter, Roche's April 23, 2009 submission proposed the following revisions to the DOSAGE AND ADMINISTRATION/Pediatric Patients subsection (~~strikethrough~~ = deletion, underline = addition)

> **DOSAGE AND ADMINISTRATION**/Pediatric Patients subsection
>
> **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 ~~infants less than 3 months old or~~ weighing less than 20~~5~~ kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

Electronic Labeling Comparison:

The content of labeling for the package insert submitted on April 23, 2009, for NDA 19-591/S-027 was electronically compared with the labeling approved on September 23, 2008, for this NDA.

The final revisions to the Lariam® (mefloquine hydrochloride) Tablets, 250 mg labeling from supplement NDA 19-591/S-027 are as follows: (~~strikethrough~~ = deletion, underline = addition)

1. **DOSAGE AND ADMINISTRATION**/Pediatric Patients subsection

   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 ~~infants less than 3 months old or~~ weighing less than 20~~5~~ kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. The tablets may be

crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

2. **DOSAGE AND ADMINISTRATION**/Pediatric Patients/Malaria Prophylaxis subsection

Malaria Prophylaxis

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

30 to 45 kg: 3/4 tablet
20 to 30 kg: 1/2 tablet
~~10 to 20 kg: 1/4 tablet~~
~~5 to 10 kg: 1/8 tablet~~~~*~~

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

Experience with Lariam in pediatric patients ~~infants less than 3 months old or~~ weighing less than 20 ~~5~~ kg is limited.

Revised: Month/Year ~~September 2008~~

Review:

Based on the electronic labeling comparison between the most recent labeling for the package insert approved on September 23, 2008, the only additional revisions to the labeling were proposed to revise **DOSAGE AND ADMINISTRATION**/Pediatric Patients subsection. This change was deemed acceptable by Dr. Vargas-Kasambira in his Medical Officer Review dated, May 21, 2009.

This labeling supplement proposed revisions to the package insert that include text to accurately detail the use of Lariam® (mefloquine hydrochloride) Tablets, 250 mg in the pediatric population for both malaria treatment and malaria prophylaxis.

Dr. Vargas-Kasambira's January 15, 2009 review of Roche's June 12, 2008, submission included recommendations for revisions to the currently approved Lariam® labeling. A

Prior Approval Supplement Request letter, outlining the revisions in Dr. Vargas-Kasambira's January 15, 2009 review, was sent to Roche on March 4, 2009.

In response to the March 4, 2009 Prior Approval Supplement Request Letter, Roche submitted S-027 on April 23, 2009.

In addition to the revisions to the Lariam® labeling requested in the March 4, 2009, Prior Approval Supplement Request Letter, Roche proposed further revisions to the labeling in the **DOSAGE AND ADMINISTRATION**/Pediatric Patients subsection in their April 23, 2009 submission.

In his review dated May 21, 2009, Dr. Vargas-Kasambira agreed with the revisions to the Lariam® labeling in the April 23, 2009, submission and recommended approval of this supplemental application. Dr Vargas-Kasambira states in his May 21, 2009, Clinical review, "The applicant's revised version submitted on April 23, 2009 is acceptable."

Conclusions/Recommendations:

In summary, the prior approval labeling supplement submitted by Roche to NDA 19-591 on April 23, 2009, proposed revisions to the package insert that would include text to accurately detail the use of Lariam® (mefloquine hydrochloride) Tablets, 250 mg in the pediatric population for both malaria treatment and malaria prophylaxis.

Dr. Vargas-Kasambira agrees with the proposed revisions and recommends approval of this labeling supplement. We also conclude that this supplemental application can be approved and recommend that an approval action be taken.

Gregory DiBernardo
Regulatory Project Manager

Judit Milstein
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Teleconference Minutes

Teleconference Date: January 14, 2008
Application Numbers: NDA 19-591
Lariam (mefloquine hydrochloride)
Sponsor: Roche
Attendees:

Roche

Lynn DeVenezia-Tobias	Senior Program Manager, Diversified Products, Drug Regulatory Affairs
Joanna Waugh	Director, Drug Regulatory Affairs
Lisa Luther	Senior Director, Drug Regulatory Affairs
Pia Suter, MD	Medical Evaluation Group - Basel

Division of Special Pathogen and Transplant Products

Renata Albrecht, M.D.	Director
Steven Gitterman, M.D., Ph.D.	Deputy Director
Joette Meyer, Pharm.D.	Acting Clinical Team Leader
Kristen Miller, Pharm.D.	Regulatory Project Manager

BACKGROUND:
An August 15, 2007 review by the Office of Surveillance and Epidemiology (OSE) recommends that changes related to neurological adverse events should be updated in the current Prescriber Information and Medication Guide for mefloquine hydrochloride based on post marketing adverse event information in the AERS database. Based on OSE's review, the Review Team recommended revisions to the Lariam labeling. On January 9, 2008, in preparation for the January 14 teleconference, the Review Team sent Roche a facsimile with recommended changes to the **PRECAUTIONS** section, **ADVERSE REACTIONS/Postmarketing** subsection, and **MEDICATION GUIDE.** On January 14, the Review Team sent Roche a table titled "Unique Cases of Disabling Neurologic Events Listing Lariam as a Suspect Medication (cases retrieved from AERS database on 18 December 2006)."

DISCUSSION POINTS:
Following introductions, Roche asked the Division to please provide clarification as to the basis for FDA's proposed revisions to the Lariam package insert (b) (4)

(b) (4)

(b) (4)

ACTION ITEMS

(b) (4)

2. Roche will confirm what information they have to support the labeling of malarial prophylaxis in pediatric patients and will update the Division within three months.

(b) (4)

Minutes Preparer: Kristen Miller, Pharm.D., Safety Project Manager
Chair Concurrence: Renata Albrecht, M.D., Director

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

/s/

Kristen Miller
1/28/2008 11:42:12 AM
CSO

Renata Albrecht
2/5/2008 08:23:00 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019591/S-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-591/S-027 **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: 027

Date of supplement: April 23, 2009

Date of receipt: April 24, 2009

This supplemental application proposes the following revisions to the package labeling:

- In the **DOSAGE AND ADMINISTRATION**/Pediatric Patients subsection, removal of information regarding experience with Lariam in infants less than 3 months old or weighing less than 5 kg and updating this information to include text that is supported by current data.

- In the **DOSAGE AND ADMINISTRATION**/Pediatric Patients/Malaria Prophylaxis subsection, removal of dosing recommendations for pediatric patients less than 20 kg in body weight and updating this information to include text that is supported by current data.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 23, 2009, in accordance with 21 CFR 314.101(a).

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

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Gregory F DiBernardo

5/11/2009 12:17:13 PM

S-027 Acknowledgement Letter