



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 (~~striketrough~~ = deletion and double underlined = addition):

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

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. 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,~~ Co-administration of other drugs known to alter cardiac conduction (eg, anti-arrhythmic or beta-adrenergic blocking agents, calcium channel blockers, antihistamines or H₁-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 Ridditid 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).

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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