



NDA 19-591/S-024

NDA 19-591/S-025

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

Dear Ms. DeVenezia-Tobias:

Please refer to your new drug application (NDA) for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

A. Prior Approval Labeling Supplement

Please also refer to your supplemental new drug application, NDA 19-591/S-024, dated June 30, 2008, received July 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

This supplemental new drug application provides for 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.

B. Changes Being Effected Labeling Supplement

Please also refer to your supplemental new drug application, NDA 19-591/S-025, dated August 26, 2008, received August 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

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

1. The **PRECAUTIONS/General** subsection of the labeling was updated as follows:

PRECAUTIONS

General

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.

2. The **PRECAUTIONS/ Information for Patients** subsection of the labeling was updated as follows:

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 MedGuide when Lariam is received and to carry the information wallet card with them when they are taking Lariam. The complete text 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 bed nets 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.

3. The **ADVERSE REACTIONS/Postmarketing** subsection of the labeling was updated as follows:

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.

4. The **MEDICATION GUIDE** was updated as follows:

- a. *What should I avoid while taking Lariam?*

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

In addition:

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

b. ***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.

c. The following statement was added to the end of the **Information Wallet Card**:

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

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions “**SPL for approved supplements NDA 19-591/S-024, S-025.**”

NDA 19-591/S-024

NDA 19-591/S-025

Page 5

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

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

If you have any questions, please call 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

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

/s/

Renata Albrecht
9/23/2008 04:37:22 PM