



NDA 19-591/S-022

Hoffman-LaRoche, Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug application dated July 23, 2003, received July 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lariam® (mefloquine hydrochloride) Tablets, 250 mg.

We acknowledge receipt of your submission dated August 15, 2003.

This “changes being effected” supplemental new drug application provides for following revisions to the labeling. Deleted text noted by ~~strike through~~ and additions are double underlined:

1. PRECAUTIONS

- In the **Information for Patients** subsection, the following sentences now appear first:

Medication Guide: As required by law, a Lariam Medication Guide is supplied to patients when Lariam is dispensed. Patients should be instructed to read the MedGuide when Lariam is received. The complete text of the Medication Guide is reprinted at the end of this document.

2. The Lariam Medication Guide approved on July 9, 2003 (with the additional agreed upon proposed labeling changes discussed with you via e-mail on August 4-6, 2003 as follows) has been added to the end of the package insert:

MEDICATION GUIDE
LARIAM® (LAH-ree-am)
(mefloquine hydrochloride) Tablets
to Prevent Malaria

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 at the end of this Medication Guide. Cut it out and carry it with you when you are taking Lariam.

This Medication Guide was _____ revised in August 2003. Please read it before you start taking Lariam and b)(4)----- 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 (b)(4)-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. It (b)(4)-----
(b)(4)-----There have been reports that in som-----
-----d. Some patients taking Lariam think about killing themselves, and there have been rare reports of suicides.(b)(4)-----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). (b)(4)-----
(b)(4)-----

----- However, if you use Lariam to
-----ression, restlessness, confusion
(possible signs of more serious mental problems), or you develop other serious side effects, contact a doctor or other health care provider.(b)(4)-----it may be necessary to stop taking Lariam and use another malaria prevention medicine i- ----d. If you can't get another medicine, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.

Who should not take Lariam?

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

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

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

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

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

How should I take Lariam?

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

To prevent malaria

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

malaria area, and after you return from a malaria area. If you don't have access to a doctor or other health care provider or to another medicine besides Lariam and have to stop taking it, leave the malaria area. However, be aware that leaving the malaria area may not protect you from getting malaria. You still need to take a malaria prevention medicine.

What should I avoid while taking Lariam?

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

In addition:

- **Be careful driving or in other activities** needing alertness and careful movements (fine motor coordination). Lariam can cause dizziness or loss of balance, even after you stop taking it.
- **Be aware that certain vaccines may not work if given while you are taking Lariam.** Your prescriber may want you to finish taking your vaccines at least 3 days before starting Lariam.

What are the possible side effects of Lariam?

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

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

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

What else should I know about preventing malaria?

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

may think you are well. But, the symptoms return later and then it may be too late for successful treatment.

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

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

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

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

General information about the safe and effective use of Lariam.

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

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

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

Distributed by:



Pharmaceuticals

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

27898583

Revised: August 2003

Copyright © 2003 by Roche Laboratories Inc. All rights reserved.

Information wallet card to carry when you are taking Lariam.



Lariam® (mefloquine hydrochloride) Tablets	
<p>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.</p> <p>If taken correctly, Lariam is highly effective at preventing malaria but, like all medications, it may produce side effects in some patients.</p> <p>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 as it. <u>It</u> may be necessary to stop taking Lariam and use another malaria prevention medicine instead.</p> <p>(b)(4) _____</p> <p><u>Revised: August 2003</u></p>	<p>Other medicines approved in the United States for malaria prevention include: doxycycline, atovaquone/proguanil (Malarone), 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.</p> <p>Please read the Medication Guide for additional information on Lariam.</p>

The carton labeling now includes the following statement (in red type) located next to the dosage on the front of the carton:

PHARMACIST: Provide a Medication Guide to each patient when dispensing Lariam.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling submitted on August 15, 2003. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
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/

Steven Gitterman
8/20/03 10:23:08 PM
for Renata Albrecht