

# Consumer Reports

March 2002

YOUR HEALTH

## Lariam's legacy

The most-prescribed malaria drug could produce psychiatric side effects in more than one-quarter of all travelers who take it.

"I've chased bad guys all around the world; been beat up, shot at; developed dengue fever and encephalitis," says Jim Prietsch, who has worked as a Washington, D.C., police officer and protected U.S. and foreign leaders for the State Department and the World Bank. Nothing, he adds, was as bad as what happened two years ago on back-to-back trips to Indonesia and Africa.

"I started to have panic attacks, nightmares, hallucinations," Prietsch says. "By the time I got to Africa, I thought I was going crazy. Problems got worse and worse. Finally, I had seizures--like someone was reaching inside my brain and flipping it upside down. I had no idea what was going on."

Not until a colleague from Europe saw the white pill Prietsch took once a week. "He told me, 'That's your problem--that stuff is poison.' " An infectious-disease specialist later confirmed that the cause of Prietsch's problems was most likely the pills he'd been taking: mefloquine.

Far from poison, mefloquine--made by Hoffmann-La Roche under the brand name *Lariam*--is prescribed to some 400,000 Americans each year when they travel to regions harboring malaria-bearing mosquitoes that are resistant to chloroquine, the drug long used as the primary weapon against malarial parasites. The federal Centers for Disease Control and Prevention (CDC) in Atlanta has endorsed two additional drugs as effective against chloroquine-resistant malaria--*Malarone* (made by GlaxoSmithKline) and doxycycline (a generic antibiotic made by many companies). However, the agency's brochures and web site list *Lariam* first and call the others "alternatives." *Lariam* is the drug of choice for the Peace Corps, the State Department, and the U. S. Army. It could well be given to American troops in Afghanistan and surrounding countries, where malaria season starts in May.

*Lariam* is effective in fending off a disease that each year kills about 2 million people worldwide and infects nearly 30,000 American and European travelers. It needs to be taken only once a week; the other antimalarials must be taken daily. And it costs less than *Malarone*. However,

there is increasing evidence that *Lariam* poses significant risks for many people.

- A database compiled by the Food and Drug Administration (FDA), and obtained by Consumer Reports through a Freedom of Information Act request, contains hundreds of reports of adverse reactions attributed to *Lariam*, including suicide attempts, during a single year.
- When Consumer Reports surveyed 36 travel-medicine experts from around the U.S., most favored *Lariam*; but more than one-third said they would prescribe *Malarone* as a first choice, nearly always because they viewed it as having fewer side effects.
- Recent research documented psychiatric and neurological side effects in more than one-quarter of travelers who took *Lariam*.

What's more, the handouts that accompany a *Lariam* prescription may fail to describe the risks adequately, we found when we sent shoppers to fill prescriptions.

## "ADVERSE EVENTS"

The FDA asks physicians and patients to report serious drug reactions. Since *Lariam's* introduction in 1989, thousands of reactions attributed primarily to the drug have been reported. (Because reporting is voluntary, the FDA estimates that, as with any drug, only 1 to 10 percent of such adverse events are actually reported.)

From October 2000 to October 2001--the most recent 12 months for which figures are available--the FDA received approximately 600 reports of adverse events. The number of reports for any drug varies with the number of prescriptions written, making drug-to-drug comparisons difficult. And because some events are reported more than once, by different doctors or by both doctor and patient, it's likely that fewer than 600 people were affected by the events that were reported. Still, more than half of the reports--a higher percentage than with most drugs--included at least one psychiatric side effect, ranging from confusion to delusions. Among people for whom we were able to weed out duplicate reports were 13 who had suicidal thoughts, 4 who attempted suicide, and 1 who committed suicide.

A typical report:

*Date: 06/05/01. Age: 26. Gender: Female. Outcome: Disability. Report Source: Health professional. Reported Reaction: Anxiety, confusion, delirium, depression, hallucinations, insomnia. Product: Lariam. Role: Primary suspect.*

Dr. Leonard Sacks, a medical officer at the FDA who has investigated particularly worrisome

reports involving *Lariam*, says that although it's difficult to prove the drug caused any individual psychiatric or behavioral reaction, the agency is concerned enough that it's discussing with Hoffmann-La Roche whether the data warrant stronger cautions. Despite repeated requests, a spokesman for the company did not answer our questions about those talks, or any other questions about the drug.

In addition to the FDA data, there are numerous anecdotes about adverse reactions. "The drug has developed quite an unsavory reputation among doctors who treat travelers in the tropics as well as tour-guide operators," says Dr. Ashley Croft, a researcher in Britain's Ministry of Defense and a leading authority on *Lariam's* safety.

Consider the case of Jane D., a 40-year-old biochemist who visited Kenya last September with her husband, Robert, a physician. "After her second dose, Jane became very paranoid," Robert told us. "She cried and screamed all night that she was getting AIDS, that people were coming to get her, that dead people were talking to her. I had no idea what was going on, but the staff doctor at the lodge where we were staying took one look and said, 'This is *Lariam*.'"

Jane was given extremely high doses of diazepam (*Valium*), evacuated to Nairobi, and then sent home. Ultimately, she became so disoriented--not even recognizing her husband--that she spent a month in a psychiatric hospital. "She's home now," Robert said in December, "but not fully recovered."

Other reports have come from military personnel overseas. Some Canadian soldiers stationed in Somalia in 1992 and 1993 complained of insomnia and nightmares after taking *Lariam*. Dutch peacekeeping troops in Cambodia during the same years complained of dizziness and problems with vision and concentration. In at least some of those cases, doctors suspected that *Lariam* was the cause and switched the affected troops to doxycycline.

The Australian military generally avoids prescribing *Lariam*. Still, the U.S. Army recommends the drug for most of its troops in malarial regions; so do the armies of many foreign governments.

## **SERIOUS STUDIES**

The U.S. military developed *Lariam* in 1975; the FDA approved it 14 years later. Most studies, generally conducted on healthy young men, have found that side effects are not significantly higher with *Lariam* than with other antimalarial drugs and that psychiatric side effects are extremely rare.

But evidence against the drug from more broadly based studies has built steadily. Several surveys conducted on travelers in the mid- to late-1990s suggested that the rate of psychiatric side effects with *Lariam* was higher than previously believed. Researchers suspect that the newer findings

may be less rosy because the drug is more likely to cause problems in older people and women than in the young men previously studied.

In October 2001, European researchers provided what experts we consulted believe is the strongest evidence against *Lariam* to date: the first clinical trial in travelers, ranging in age from 4 to 80. In that trial, 483 travelers took *Lariam* and 493 took *Malarone*, a new medication that combines two drugs, atovaquone and proguanil. (*Malarone's* manufacturer paid for much of the trial's administrative costs, but independent researchers designed the study and analyzed the results, which were published in a respected, peer-reviewed journal.)

The patients did not know which medicine they received; neither did their doctors. After 60 days, 139 (29 percent) of the people who took *Lariam* reported at least one psychiatric side effect, and 92 of them (19 percent) rated those effects moderate or severe. Both percentages were roughly double those reported by the *Malarone* group. Side effects were so severe in the *Lariam* group that 5 percent of the patients stopped taking the drug, four times the rate of patients who dropped out of the *Malarone* group. People who don't take their medication, of course, are susceptible to malaria.

"That trial convincingly showed not only that the neuropsychiatric side effects are real, but that they're common, especially compared to other malaria preventives now available," says Dr. Croft.

Any side effects usually disappear a few days after a person stops taking *Lariam*, the evidence shows. But in some people, effects last weeks or even months, possibly because *Lariam* lingers in your system: It takes 15 to 33 days for half the drug to leave the body.

## EXPERT OPINION

Some experts are reexamining their advice in light of the accumulating evidence about *Lariam*. Dr. Monica Parise, medical officer in the malaria epidemiology branch of the CDC, told us that the agency is reassessing its malaria-prevention recommendations.

In our survey of travel-medicine experts in the fall of 2001, *Lariam* was usually cited as the drug of choice because of its effectiveness. Yet more than one-third of the respondents preferred to prescribe *Malarone*. All but one cited fewer side effects as the key reason. (One expert chose *Malarone* because of its effectiveness--and indeed, several studies have shown it is as effective as *Lariam*.) General-practice doctors, who may be less familiar with the side effects of *Lariam*, are apparently more likely than travel doctors to prescribe it. In the most recent 12 months for which data are available, nearly seven times as many prescriptions were written for *Lariam* as for *Malarone*.

Most worrisome, people who receive those prescriptions for *Lariam* may not be informed of the

drug's potential risks, as we note in *What drugstores don't tell you*.

## RECOMMENDATIONS

Given how dangerous malaria can be, no one recommends doing without an antimalarial drug in regions where the disease is prevalent. "Which one you take," Dr. Croft says, "depends on where, when, and how long you travel, as well as your medical history, your preference, and your finances."

Avoid *Lariam* if you have epilepsy, seizures, a heart-rhythm disorder, or psychiatric problems, including ongoing depression. Avoid *Malarone* if you have kidney failure, and doxycycline if you have liver disease or are pregnant.

*Lariam* doesn't produce side effects in everyone, and both alternatives can have side effects, too. *Malarone* and doxycycline can cause nausea; doxycycline can also cause sun sensitivity and yeast infections in women. Doxycycline is unlikely to cause psychological effects; *Malarone* can cause vivid dreams, insomnia, and dizziness.

According to Scott-Levin, a market-research firm that tracks the drug industry, a week's dosage of *Malarone* costs about \$33; *Lariam*, \$10; doxycycline, \$3. Whatever drug you're prescribed, ask the doctor and pharmacist for a complete list of possible side effects. If the doctor prescribes *Lariam*, consider starting to take it two weeks before departure, to see how you react to it. To report an adverse reaction, log onto [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call the FDA at 800-332-1088. For detailed information about any drug, visit [www.medlineplus.gov](http://www.medlineplus.gov).

To determine whether you will need protection against malaria while traveling, and for ways to guard against mosquito bites, visit the CDC's Travelers' Health web site, [www.cdc.gov/travel](http://www.cdc.gov/travel).

- o What drugstores don't tell you Forums