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UPI Investigates: Lariam and suicide

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WASHINGTON, May 21 (UPI) -- Mounting evidence suggests the anti-malaria drug Lariam -- prescribed to Peace Corps volunteers, travelers and U.S. soldiers -- has triggered mental problems so severe that in a small percentage of users it has led to the ultimate side effect: suicide.

Lariam -- also known as mefloquine -- is a product of Hoffmann-La Roche, a giant Swiss pharmaceutical company with U.S. headquarters in Nutley, N.J. Lariam has been prescribed to more than 22 million people worldwide since 1985. It was cleared for use in the United States in 1989.

Some health experts charge that neither patients nor doctors in the United States are being adequately warned about the risk of suicide from taking Lariam, which is prescribed by U.S. doctors 1,000 times every day.

In a two-month investigation, United Press International reporters found:

- * In thousands of pages of internal Roche documents obtained by UPI spanning a decade, the company tracks increasing reports of suicides, suicidal behavior and other mental problems among Lariam users.
- * A 1994 Roche safety report notes that because Lariam can cause depression and depression can lead to suicide, "a causal link to Lariam can in theory not be ruled out."
- * Dozens of soldiers, Peace Corps volunteers, other government workers and private travelers, in interviews with UPI, court filings, case studies and reports from medical personnel, said they had no history of mental illness before taking Lariam, but then attempted or considered suicide. Families gave similar accounts of several who succeeded in killing themselves.
- * An activist group said it has heard from 120 Somalia veterans who had problems they attributed to Lariam, including suicide attempts. Military medical officers in charge of giving Lariam to more than 20,000 U.S. troops there in 1992 and 1993 said they saw no evidence of a problem. Troops in Afghanistan are taking Lariam as the weather warms, but some officers on the ground in Afghanistan said they themselves were not taking it because they feared liver damage.
- * The U.S. Food and Drug Administration's files contain reports over the past four years alone of 11 suicides, 12 suicide attempts, 41 cases of thinking about suicide and 144 cases of depression among Lariam users.
- * A statistical analysis of FDA data, commissioned by UPI, indicates that Lariam users are five times more likely to report having mental problems that could lead to suicide than those taking a different drug -- the antibiotic doxycycline -- also used to prevent malaria.
- * More than a dozen lawsuits over the alleged effects of Lariam have been filed in the United States -- at least seven against Roche, and the others against doctors or pharmacists. Some have been dismissed or settled out of court.

"There have been a number of cases of suicide, both in the United States and abroad, that are clearly associated with the use of Lariam," said Susan Rose, an adjunct assistant professor at George Washington University's public health school and an attorney who has represented plaintiffs suing Roche.

No one has won a case against Roche alleging Lariam caused a suicide, but Rose, speaking as an advocate for plaintiffs with a background in public health, said: "Suicidal thoughts and impulses are far more commonly experienced than the current product information sheet would lead physicians or consumers to believe. This is critical, life-saving information that must be conveyed now to travelers and the medical community."

Roche consistently has denied there is evidence showing taking Lariam can cause the kinds of mental problems that could lead to suicide. The company said Lariam is an important drug for combating malaria.

"Believe me, as a company we support this drug and stand behind it," said Roche spokesman Charles Alfaro. "Roche works with all regulatory authorities both before and after product approval to ensure recommendations for

product use that take into account current medical evidence."

"It (Lariam) remains a drug of choice for the prevention and treatment of malaria by such leading health authorities as the CDC (Centers for Disease Control and Prevention), the WHO (World Health Organization) as well as many travel organizations, clinics, and individual physicians," Alfaro said.

Asked whether Lariam could cause suicide, Alfaro said he could not answer because it was an issue in pending litigation.

Adverse side effects of drugs are voluntarily reported by physicians and others to the FDA and drug companies. The FDA said in general, drug side effects are reported in only 1 percent to 10 percent of cases.

Dr. Raymond Woosley, dean of the University of Arizona Medical School and an expert on drug side effects, said he would be "very comfortable" with an estimate of actual suicides 100 times greater than the 11 reported to the FDA in the past four years.

Experts said the FDA lacks the resources to follow up on side effect reports even for drugs recently approved.

"I would be very surprised if there's very much surveillance of this drug (Lariam) at all," said Woosley. "It's 12 years old. The FDA probably wouldn't have the people power. They're understaffed, they have inadequate resources and they're putting out fires and looking at new drugs."

The FDA said in a written statement to UPI it would have taken action if it had confirmation Lariam caused suicide. But the FDA said confirmation required either biological or statistical evidence.

While the FDA database included reports of 11 suicides among Lariam users, all but one of them outside the United States, the agency said "to 'blame' Lariam for all these cases is not scientifically justified."

"On balance we believe the risk of such rare and poorly substantiated events is more than offset by the benefit in preventing malaria deaths," the FDA statement said.

Under the "less frequently reported adverse events" section on Lariam's label, Roche added in 1999: "Suicidal ideation (thinking) has also rarely been reported, but no relationship to drug administration has been established." These labels in the United States come as fine-print package inserts that patients do not automatically receive.

Other nations have acted to ensure consumers receive warnings of possible adverse reactions to Lariam --which is chemically related to the quinolone group of antibiotics, long documented as capable of causing mental problems.

In 1997, the British Malaria Advisory Committee, for instance, stopped recommending Lariam for trips of two weeks or less. Patients who do take it receive a written warning that includes: "Effects on nervous system: psychiatric reactions which may be disabling and last for more than several weeks. These include unusual changes in mood or behavior, feelings of worry or anxiety, depression, feelings of persecution, crying, aggression, restlessness, forgetfulness, agitation, confusion, panic and hallucinations. If you experience any of these effects you should immediately stop taking Lariam and consult a doctor."

In Canada, "Information for the Consumer" from Roche states: "It is best to avoid alcoholic drinks during treatment with Lariam." No such warning appears on the U.S. label despite increasing concerns alcohol can be a problem when mixed with Lariam.

"I think alcohol, in particular, can be a confounder with Lariam," said Dr. Alan Magill, a Walter Reed Army Medical Center official who was in charge of the health of U.S. soldiers deployed to Somalia in the early 1990s.

Magill said he saw no major side effects among troops taking Lariam. By contrast, Jeanne Lese, information manager of the activist group Lariam Action, said "more than 120 Somalia vets have contacted us about Lariam and 11 said they have considered or tried suicide -- one tried it 10 times and shot herself twice" but survived.

UPI interviewed half a dozen of the Somalia veterans who had contacted the group. They spoke of marked personality changes in themselves and others, suicidal thoughts and suicide attempts, flashbacks, nightmares and paranoia. One said that most soldiers drank alcohol daily, aggravating the side effects. Another said his doctor in the United States did not seem aware of Lariam side effects.

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The CDC declared Lariam its "drug of choice" in March 1990 and that fall recommended doses of Lariam be doubled from once every two weeks to once a week, after the first four weeks of weekly doses. Because the CDC is the guidepost for malaria prevention in the United States, other government agencies, private travel clinics and doctors quickly adopted the regimen.

That recommendation followed a survey of 562 Peace Corps volunteers, led by the CDC's chief malaria expert, Dr. Hans Lobel. The study results eventually appeared in the Journal of the American Medical Association in January 1991.

"No serious adverse reactions were observed," Lobel wrote of the volunteers who took Lariam. Because some of those volunteers contracted malaria, a sometimes-deadly disease, Lobel said weekly doses of Lariam "should be considered."

Some doctors said the U.S. government never should have used the Peace Corps study as a basis for increasing doses of Lariam.

The dose increase was "an astonishing piece of non-evidence-based science," said Dr. Ashley Croft, a British army lieutenant colonel who has done extensive research on Lariam and who said he believes it can cause serious mental problems that increase as doses rise.

"It is really quite amazing that this doubling-the-dose policy - which of course doubled the company's profits at a stroke - was immediately adopted everywhere, and on the basis of such a flawed study," Croft said.

He said he believes that in the Peace Corps study, some of the volunteers may have quit taking the drug because it bothered them, and got malaria as a result.

In a 1994 internal Roche document, the company said an evaluation by Lobel, director of the CDC's malaria prevention program at the time, indicated the Lariam package insert was adequate.

"According to a consultant expert in the field of malaria, Dr. H. Lobel, CDC, Atlanta, the current package insert adequately addresses suicidal ideation under 'depression', in view of the isolated reports received," the 1994 Roche safety report read. "No change in the package insert is required at present."

Roche declined to discuss Lobel's recommendation with UPI or his status in the 1994 report, which called him a consultant expert. CDC rules prohibit compensated or uncompensated consulting without express written permission.

CDC spokesman Tom Skinner said the agency does not have records indicating Lobel received such permission, if it was needed.

"I have never been a consultant for Roche," Lobel told UPI. He did say he often worked as a consultant for other organizations, such as the World Health Organization, but not for Roche.

Skinner said the CDC had opened an ethics inquiry in the issue. "There is a formal process the CDC must go through to determine if any action needs to be taken," Skinner said.

UPI reviewed thousands of pages of Roche's internal safety reports for the decade after the drug dose was increased. "Eight patients attempted suicide, three by leaping out a window," reads one Roche safety report of side effects documented through 1993, in a section titled "Depression with Suicidal Tendency."

A 1994 safety report said because Lariam can cause depression and depression can lead to suicide, "therefore a causal link to Lariam can in theory not be ruled out." It went on to say reports of suicide attempts were rare and fell within the incidence of suicides among the general population.

That document also noted "the first report of suicide with the use of Lariam" and went on to say "Roche has received eight reports of attempted suicide, four of them associated with depression (previous (medical) history unknown)."

"Fourteen additional patients reported suicidal thoughts. All were associated with psychiatric disturbances" including depression, the 1994 report said.

That first report of suicide in 1994 was of Canadian Army Cpl. Scott Smith, who was stationed with the United Nations in Rwanda. Smith reported having hallucinations he attributed to Lariam months before his death.

In an October 1994 interview with a journalist on a flight from Somalia to Rwanda, Smith said the difficulties began when he was stationed in Somalia. The writer, a correspondent for Canadian Transportation Logistics, reported the conversation in the December 1994 edition of the magazine. It appeared shortly before Smith's death.

"Cpl. Scott Smith ... is one of the unfortunate ones to react to the malaria medicine everyone has to take. He experiences hallucinations," the magazine said.

The Roche safety report on Smith made no mention of the reported hallucinations and said use of Lariam was "more likely coincidental" to the suicide, especially since Smith had been drinking.

A Roche safety report for 1998 -- the last year examined by UPI -- said of Smith: "There is insufficient information for assessment of this case. The Canadian military has not confirmed this information nor have they provided any clarification. All information has been compiled from the media," it said.

Canadian Member of Parliament John Cummins studied reports of Lariam side effects among Canadian soldiers. Cummins said Roche should have known and stated in its report that Smith had hallucinations he attributed to Lariam.

"I think that is gross negligence on their part," Cummins told UPI.

But Cmdr. David Carpenter, head of the Canadian military's communicable disease control section, said Lariam remains the drug of choice "where indicated" by the kind of malaria and whether the disease is resistant to other drugs. Asked about the Smith case, Carpenter told UPI, "I vaguely have heard of it," but he said a government review found "there was nothing to substantiate it was mefloquine-related."

He said Lariam's rare psychiatric side effects are well-known and troops are carefully monitored for bad reactions, in which case they are generally given doxycycline. But he said, "When you're doing travel medicine for the military as I do, you have to weigh the real and often very common risk of getting malaria against the risk of psychiatric problems. Usually the balance is toward preventing malaria."

The 1994 Roche safety report also attributed suicidal tendencies chiefly to factors such as "the progressive break down of traditional values" and family structure, substance abuse and unemployment, not to Lariam use.

By 1998, Roche reported that four suicides during the year might be connected to Lariam, but said, "No causal relationship could be established." That year, it added a new appendix to the annual safety report entitled, "Special Review: Lariam and Suicide, Suicide Attempt and Suicidal Ideation" (thinking about suicide). The report said the company was tracking seven suicides, 13 suicide attempts, 46 cases of thinking about suicide and 3,419 "psychiatric events."

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For the men and women troubled by Lariam, those dry statistics were very real and sometimes deadly experiences.

"I was a raving, crazy lunatic," Martin Giannini said in an April telephone interview with UPI from Dublin, where he is trying to rebuild a life he says was shattered by Lariam. He took Lariam from June 1995 through September 1996 as a Peace Corps volunteer while in Togo in West Africa.

He said his mental problems started with nightmares, headaches and dizziness. He said his condition the next two months quickly deteriorated into an enveloping psychosis that required him to be evacuated.

"I just went to pieces," Giannini said. "I'd been telling (Peace Corps medical personnel) since Day One that I had been having problems with this drug."

Back in the United States, Giannini suffered from hallucinations. He heard voices. His mental problems climaxed in a three-day high-speed car trip that led him from Oklahoma to Illinois and into Wisconsin, where after a car crash he was found wandering in the woods. He has been hospitalized several times. He said he considered suicide.

"There were times ... It was amazing I survived."

Peace Corps medical officials said reports of mental problems among volunteers are due to the onset of schizophrenia that can show itself in the early 20s, when most volunteers join up, but not because of Lariam.

"We do get people who develop schizophrenia in the Peace Corps, but it is not associated with mefloquine," said Russell Gerber, chief of the epidemiology unit at the Peace Corps.

Giannini sought back wages from the U.S. government, because the Peace Corps is a federal agency. In March 1998, the U.S. Department of Labor wrote Giannini a letter saying the department agreed to pay his medical expenses and compensate him for lost wages, "for a single, sustained, but acute psychotic reaction to mefloquine use" that lasted a full year.

UPI talked to 32 doctors, scientists and other experts, and 27 people who said they suffered adverse side effects from Lariam use. UPI reporters also reviewed dozens of e-mails from around the world -- from soldiers, travelers and medical experts in the field -- about problems with Lariam, as well as published reports.

Some examples:

-- Francis Macleod Matthews, a 37-year-old lawyer who had taken Lariam a year earlier but continued to be troubled by bad dreams, threw himself off the roof of an apartment building in London. The coroner, Paul Knapman, ruled the

death a suicide and said, "It is more likely than not that Lariam played some part," according to the Times of London.

-- Irish tourist Malcolm Edge, 27, was found hanging in a hotel room in Ho Chi Minh City, Vietnam, in 2000; he was taking Lariam. Edge had undergone a startling personality change on the trip, according to a traveling companion. The Dublin coroner notified the Irish Medicines Board that "concerns were expressed at the inquest in relation to possible psychotic reactions to Lariam," but the coroner made no conclusion whether Lariam was a contributing factor in the death.

-- In Australia, John O'Callaghan, 29, committed suicide after being treated with Lariam for malaria he contracted on a surfing trip to Indonesia. "Almost immediately," his mother Jan wrote in an e-mail to the group Lariam Action, "he suffered severe neuropsychological and physical side effects. We did not know he was suffering from mefloquine toxicity. He had no history of these (physical and mental) illnesses. For a couple of years he tried to return to his previous healthy lifestyle. Finally, in September 2000, he took his own life." He left a note:

"I know God will forgive me. No one could live with how I am feeling now. I know I will never forgive the bastards that gave me Lariam. I am now the same as when I first had it -- fully spinning can't even walk properly - the walls are moving. My head feels like someone let a box of ants in it, extreme pain in my head. I am fully losing it. What does the future hold -- 'psychiatric wards' no way. I know I've always been a little bit different even before I had Lariam but since it first blew my brains apart and then settled down I have never been the same, always dazed and confused, always physically sick. I never thought this could happen to me. Sorry Mum, Dad"

O'Callaghan's account of symptoms mirrors those of several others: Charles Perry, who committed suicide in Ohio in 1999, spoke of a relentless pain at the base of his cranium, said his wife, Linda: He would put his head on the table and hold his hand over the base of his skull, saying, "This is where it hurts." (Linda Perry sued Roche for alleged failure to warn about side effects, including suicide. The lawsuit recently was settled out of court. The terms were not disclosed).

Rosemary Waller of Cincinnati kept a diary of symptoms that developed after she took Lariam in the summer of 1997. Her entry for May 3, 1999, reads: "Scalp burning, gripping intensified into worst-ever headache." On June 8 she noted "almost continuous scalp sensations of burning, crawling, gripping, hole-boring through in one of several spots on scalp."

Elisa von Joeden-Forgey, who went to Africa in 1995 as part of her doctoral work at the University of Pennsylvania, described "this horrible burning sensation in the back of my head, in my lower cranium, this burning, constant burning."

-- In a March e-mail from Nairobi, Kenya, psychiatrist Dr. Lorin Mimless wrote of treating seven patients with what he said were clear Lariam reactions.

Among the cases he describes is a 32-year-old man he saw a year ago who he said had no history of psychiatric problems and was on no other medicine. He said the man became paranoid and over a two-day period his problems "developed into a full-blown psychosis requiring hospitalization in Britain. The patient on arrival tried to kill himself by hanging."

Mimless said he saw the man recently and "he still had significant psychiatric symptoms -- depression, occasional paranoid thoughts when anxious, and suicidal thoughts that would come and go not connected to the depression. He could not explain them but they would come once or twice a month, sometimes for a day, sometimes for a few hours. He would attribute them to Lariam, although he always had the fear they would not go away."

A researcher who formerly reviewed Lariam side-effect reports at Roche said he now believes the company has been too hesitant to alert physicians and consumers to side effects that emerged after a drug had been approved.

"Roche has developed an attitude of not adjusting the information it supplies to physicians and patients about the performance and safety characteristics of their drugs," said Dr. Donald H. Marks, former associate director of clinical research at Roche. Marks said he left Roche in 1991 to take a promotion to director at another company.

Marks said there is "ample reason" to believe Lariam causes suicide. Marks said Lariam can cause "spontaneous neurological activity" and "irritation of certain sensitive areas inside the brain" that could lead to suicidal behavior long after someone stops taking it.

Roche did not respond to UPI's written questions about Marks' comments. Alfaro, the Roche spokesman, said: "Roche takes the issue of safety very seriously and is diligent in monitoring the safety of all its drugs."

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Two statistical studies of FDA data commissioned by UPI showed a far higher incidence of problems that could lead to suicide in people taking Lariam than in those taking doxycycline, an antibiotic recommended by the CDC as another drug to prevent malaria.

The studies' authors said that because both drugs are recommended by the CDC for prevention of malaria, a comparison of reported mental problems among users of both drugs is valid.

The FDA said in a statement to UPI that suicide rates of patients taking doxycycline and Lariam cannot be validly compared because most people treated with doxycycline receive it for acute bacterial infection -- a much shorter therapeutic regime -- and not for prevention of malaria.

The FDA also said doxycycline has its own drawbacks: it cannot be used in children, sensitizes people to the sun, has to be taken daily while Lariam is taken weekly, and causes anorexia, nausea and vomiting.

Doxycycline is the malaria preventive President Clinton was prescribed when he traveled to India and Pakistan in early 2000.

PharmaGenesis of Bethesda, Md., and Fibonacci Group, a Philadelphia-based consulting group, conducted two separate studies of FDA raw data. Both firms do work with attorneys suing drug companies.

In one study for UPI, PharmaGenesis determined people taking Lariam were five times more likely to have reported mental problems that could lead to suicide than people taking doxycycline. In the other, Fibonacci examined the FDA data and calculated the rate of side effects per prescription. It found a 150 times greater rate of depression and a 40 times greater rate of suicide attempts among Lariam users compared with doxycycline users.

The studies did not find a single successful suicide associated with doxycycline in the past four years, even though doxycycline, an antibiotic, is prescribed 25 times more often than Lariam, which is used only for treatment and prevention of malaria. Lariam is prescribed some 350,000 times a year, doxycycline is prescribed 9 million times a year for a variety of medical reasons, according to data from IMS Health, a healthcare information company.

Experts on drug side effects warned the FDA's data cannot solely be used to draw conclusions about drug safety, but they agreed analyses from 1997 forward are best because at that point the agency began tracking suicides.

The PharmaGenesis analysis found three reports involving suicide prior to 1997 were "high probability," based on a review of the psychiatric side effects reported in those patients.

Roche's documents said seven suicides were reported by the end of 1998 as associated with Lariam use, including one in 1994, two in 1997 and four in 1998.

Roche and Lobel have said mental problems in those taking Lariam might be related to increased stress during travel. Keith Altman of Fibonacci Group said he thinks the 1997-2001 data debunk that assertion -- particularly considering the different prescription totals for the two drugs.

"If you're looking at rates-per-prescription, you're talking about a 40 times greater rate of suicide attempts in Lariam than in doxycycline," Altman said. "Look at depression: the rate of depression is 150 times greater in Lariam. I just can't see a 150-times-greater rate of depression when you consider that a lot of these people are happy they're going on a trip."

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A clinical study in October 2001 in the peer-reviewed Clinical Infectious Diseases journal showed 29 percent of travelers taking Lariam complained of neuropsychiatric side effects and that 5 percent were so bothered they quit taking the drug altogether. The "randomized controlled trial" was done among 976 travelers in the field.

Another drug company, Glaxo-Wellcome, funded the study and used Lariam as a control pill to gauge the safety of its own anti-malaria drug, Malarone, approved by the FDA in July 2000. FDA data shows two suicides reported among Malarone users.

Croft, the British army lieutenant colonel, said the Glaxo-Wellcome study shows the U.S. government warnings for Lariam "need to be revised urgently now that there is good evidence for the potential harms of mefloquine."

Roche also makes Accutane, the popular acne drug that has also been associated with reports of suicide mainly among young people. In one high-profile case in Florida, the mother of Charles Bishop filed suit against Roche April 16, alleging Accutane made Bishop, 15, fly a Cessna plane into a Tampa high-rise and kill himself in January.

Roche and some drug experts have both said there is no concrete scientific evidence to link Accutane to suicide. Unlike its approach with Lariam, however, Roche in May 2000 put new language on the Accutane label warning of suicide risks, almost 20 years after the FDA approved the drug in 1982.

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An alleged failure by Roche to provide adequate warning of Lariam side effects, including suicide, was at the heart of

the lawsuit filed by Linda Perry in federal court in Ohio. The suit recently was settled. Charles Perry, 54 and a father of seven with no history of mental illness, took Lariam in 1998 during an African safari to celebrate his 30th wedding anniversary with his wife, Linda, a nurse.

The suit alleged the information provided by the pharmacy that filled their Lariam prescription warned only of possible "nausea, diarrhea, stomach upset, vomiting, dizziness or vision problems" and to "report difficulty breathing."

Linda Perry contended that before her husband took the fourth pill, he was hallucinating. She said after returning to Ohio, they followed directions and took another four pills over the next four weeks. But Charles Perry spiraled into psychosis. He was hospitalized in the weeks before he killed himself with a shotgun in January 1999. His psychiatrist filed a report with the FDA blaming the suicide on Lariam.

Roche contended in court that there was nothing to prove Lariam can cause suicide. "The proposition advanced by plaintiff here -- that Lariam causes such profound psychotic episodes that suicide is a known or knowable consequence of Lariam use -- is simply not supported by competent medical and scientific literature," Roche lawyers wrote in a court filing in January.

"No well-controlled clinical study supports such a causal relationship. As such, it is not generally accepted in the medical community that Lariam use leads to suicide."

But Perry's widow contends there is a connection. She said they would have stopped taking Lariam if they had been clearly warned of the risks. In an interview in the months after her husband's death, she said: "There was absolutely nothing on the bottle, from the pharmacy or from the health department that would have indicated that we should stop taking this."

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(Research: Oliver Read)

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