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THE OVERVIEW

## A Widely Used Arthritis Drug Is Withdrawn

By GINA KOLATA

### Correction Appended

The drug company [Merck](#) announced yesterday that it would stop selling its arthritis and pain medication Vioxx, currently taken by close to two million people worldwide, because a new study found that it doubled patients' risk of heart attack and strokes.

Vioxx has been a blockbuster for Merck, with sales of \$2.5 billion last year, and has been widely marketed as a safe alternative to drugs like aspirin, which can cause ulcers and gastrointestinal bleeding.

The decision to remove the drug from the market, the largest drug recall in history as measured by sales, comes as Merck has been struggling to find new drugs for its aging product line.

Vioxx represented about 11 percent of the company's revenue last year. Merck stock plunged 27 percent yesterday on the news, reducing the company's stock market value by \$25 billion and helping pull the Dow Jones industrial average down by 0.6 percent for the day.

The company decided to withdraw the drug from pharmacy shelves after a study that it had hoped would show that Vioxx prevented colon polyps, which can sometimes become cancerous. Merck quickly ended the trial after the results of the study showed last week that the drug led to heart attacks and strokes.

The risk was small - 15 cases of heart attack, stroke or blood clots per thousand people over three years compared with 7.5 such events per thousand patients taking a placebo. But the data were so unambiguous that Merck told federal regulators this week that it had halted the trial and would take the drug off the market; it announced that decision yesterday.

"What we found in this study is that beginning after 18 months, there was a discernible and unexpected increase in cardiovascular disease rates," Dr. Peter S. Kim, president of Merck Research Labs, said in an interview yesterday.

There had been hints before that the drug might increase the risk of heart attacks and strokes, but the studies were not definitive and the company said it had not been convinced that the risk was real, although it did revise the drug's label two years ago to include that possibility.

This time was different.

"What we saw was stunning," Dr. Kim said. "We certainly don't understand the cause of this effect, but

it is statistically significant and it indicated that there is an issue."

Dr. Kim said the decision came on Monday, after a series of urgent teleconferences with medical experts over the weekend. On Tuesday, company officials went to the Food and Drug Administration and said it was withdrawing the drug. The decision was the company's alone, and there was no pressure from the F.D.A., which said it was surprised by Merck's move but agreed with it.

"We think Merck did the right thing," said Dr. Steven K. Galson, the acting director of the F.D.A.'s Center for Drug Evaluation and Research.

Not everyone who takes Vioxx does so for 18 months or longer. Or even daily. Some arthritis patients take it only during flare-ups. And other people might take it only for several months, after a sports injury, for example. Medical experts say that it is safe for patients to abruptly stop taking Vioxx, adding that there are many alternatives to the drug, including cheap over-the-counter drugs. One of those, aspirin, is much cheaper than Vioxx, which has sold for \$2.50 or more a pill. Vioxx provides about the same pain relief as aspirin, although studies showed that patients taking Vioxx were less likely to develop ulcers or gastrointestinal bleeding.

There are also two prescription drugs, Celebrex and Bextra, both made by [Pfizer](#), which are similar to Vioxx but have not been shown to pose cardiovascular risks. That, and Pfizer's extensive advertising, may help explain why sales of Celebrex have lately been twice those for Vioxx. The F.D.A. says, however, that studies of Celebrex and Bextra have lasted only a year, and the Vioxx study found risks only after people had taken it for 18 months.

Asked in a telephone news conference if the agency will start requiring longer-term studies for drugs of this class, Dr. Galson said no decision had been reached.

"It's too early to say right now, but obviously we will be more interested in long-term data," he replied.

Dr. Kim of Merck said he first learned of the new data on heart attacks and strokes on Thursday evening last week, when he got a call from an independent committee of scientists who were monitoring the colon polyp study. "They recommended we stop the study," he said.

"On Friday, I looked at the data with my team," Dr. Kim said. "The first thing you do is review the data. We did that. Second is you double-check the data, go through it and make sure that everything is O.K." At that point, he said, "I knew that barring some big mistake in the analysis, we had an issue here."

"Around noon, I called Ray Gilmartin and told him what was up," Dr. Kim continued, referring to Merck's chief executive. "He said, 'Figure out what was the best thing for patient safety.' We then spent Friday and the rest of the weekend going over the data and analyzing it in different ways and calling up medical experts to set up meetings where we would discuss the data and their interpretations and what to do."

On Sunday night and Monday morning, Dr. Kim and his team spoke to researchers doing studies and to medical experts in rheumatology, cardiology and gastroenterology.

Some, he said, told him to take the drug off the market right away. Others could not decide what recommendation to make. Rheumatologists, however, told him that there were patients who needed the drug.

By late Monday morning, Dr. Kim had made his decision. "We were going to withdraw," he said.

He told Mr. Gilmartin and got his agreement. On Tuesday, Merck notified its board and that afternoon the company told the F.D.A. On Wednesday, the company began notifying regulatory agencies in other countries. Yesterday morning, Merck made its public announcement.

Although Mr. Kim said he was stunned by the data, others were less surprised.

The possibility that Vioxx might increase the risk of heart attacks first emerged three years ago, in a Merck study of 7,000 patients with rheumatoid arthritis. The company was asking whether those taking a high dose of Vioxx, 50 milligrams a day, had fewer gastrointestinal side effects than those who were randomly assigned to take naproxen.

The results showed that the Vioxx patients had half the incidence of gastrointestinal complaints, but it also indicated that they had five times the number of heart attacks - five per thousand patients as compared to one per thousand with naproxen.

The question was why. It could be, as some cardiologists argued, that Vioxx caused heart attacks. Or it could be, as Merck argued, that Vioxx was neutral, while naproxen actually reduced the likelihood of a heart attack.

In April 2002, at the request of the Food and Drug Administration, Merck added the study's finding about heart attack risk to the drug's label.

Several other studies followed. One looked at a million Medicaid patients; another at 1.4 million patients enrolled in Kaiser Permanente's health care plans; another at more than 50,000 Medicare patients. Each found more heart attacks and strokes with Vioxx, but medical experts differed over how to interpret the data.

Dr. Eric Topol, a cardiologist at the Cleveland Clinic, writing in medical journals, argued vehemently that Vioxx and others in its class were not worth taking. He said they had "marginal efficiency, heightened risk, and excessive cost" compared with drugs like aspirin.

Dr. Daniel Solomon, a rheumatologist and epidemiologist at Brigham and Women's Hospital in Boston, said yesterday that he was convinced enough by the data that he stopped prescribing Vioxx two years ago.

Dr. Solomon scoffed at Merck's assertion that the new data were unexpected. "I was like, 'Please. Really,' " Dr. Solomon said.

But others, including Dr. Michael Lockshin, an arthritis specialist at the Hospital for Special Surgery in New York, were less certain. Dr. Lockshin said that, until now, "the data were quite minor" to indicate that Vioxx was causing a problem. The original study's findings had an alternative explanation, he said, and the other studies were complicated by the fact that they lacked enough rigor to make the case.

The new data, however, convinced him. Even if Merck had not withdrawn the drug, he would no longer prescribe it, Dr. Lockshin said.

"Although the numbers are not huge in terms of risk, these are the things that I, looking at it as a practitioner, couldn't say, 'Oh, well. This drug is as safe as another.' "

He added, however, that some of his patients might have difficulty finding an alternative to Vioxx. Pain relief, he said, is idiosyncratic and unpredictable. "Some patients respond beautifully to one drug and not to another."

And some patients are simply reluctant to give up a drug that worked for them.

Dr. Jerry Lynn, a retired dentist who lives in Manhattan, said Vioxx was the only drug he had ever taken for his arthritic knee. "It made a big difference," he said yesterday. He still has a large supply, he said, adding, "I'll just use them until I use them up."

**Correction:** Oct. 2, 2004, Saturday

*A front-page article yesterday about Merck's withdrawal of Vioxx, its arthritis and pain medication, from the market misstated the findings of the study that led to the action. Among patients taking Vioxx, the study found 15 cases of heart attack, stroke or blood clot per thousand people per year, not over three years. Among patients taking a placebo, the study found 7.5 such cases per thousand people per year, not over three years.*

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