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Merck Pulls Vioxx From Market After Link To Heart Problems

Drug's Demise Raises Concerns About Company's Future; Loss of $2.5 Billion in Sales

Patients Are Left in Quandary

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On the morning of Sept. 24, Raymond Gilmartin, chief executive of **Merck** & Co., got the call every pharmaceutical executive dreads. Peter Kim, Merck's research chief, told him an outside panel overseeing a clinical trial of the company's painkiller Vioxx had urged Merck the night before to halt the trial and immediately stop patients from taking the drug.

The reason: Patients on the drug were twice as likely to have a heart attack or stroke as those on a placebo.

Six days after that call, Merck announced that it is withdrawing Vioxx from the world-wide market.

The drug had global sales of $2.5 billion in 2003 and more than 100 million prescriptions have been written for it since it went on the market in 1999, according to Merck. But it had been dogged for several years by suggestions that it led to heart problems. Until yesterday, Merck vehemently denied there was a connection.

The decision will put millions of patients in a quandary. About two million people are taking Vioxx now, many for arthritis. Doctors say some can switch to similar drugs such as **Pfizer** Inc.'s Celebrex or over-the-counter pain relievers such as ibuprofen and naproxen, known by the brand names Advil and Aleve. However, patients and doctors will have to weigh the various drugs' side effects, which include stomach ulcers.

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PATH TO WITHDRAWAL

Merck's Vioxx, which had sales last year of $2.5 billion, showed evidence of heart attack and stroke risks as early as 2000. A look at the path from approval to withdrawal.

• **May 1999:** Vioxx is launched in the U.S. and is marketed in more than 80 countries.
• **2000:** Trial enrollment begins for a study to determine the effect of three years of treatment with Vioxx on the recurrence of polyps of the large bowel.
• **March 2000:** Another study demonstrates that gastrointestinal

Vioxx's demise raises questions about Merck's future as a top-tier drug company and whether it might be forced into a merger, which Mr. Gilmartin has long resisted. Merck's shares plunged, erasing $26.8 billion from its market capitalization. Shares fell $12.07, or 27%, to $33 in 4 p.m. composite trading on the New York Stock Exchange. The stock is among the most widely held and is included in the 30-company Dow Jones Industrial Average. It was the largest drop in percentage terms for a Dow stock since United Technologies Corp. lost 28% in September 2001. Pfizer shares were up 1.4%.

Vioxx accounted for 11% of Merck's global sales in 2003, and its loss is expected to shave around 20% off the company's profit this year.

Once the industry leader, Merck has struggled in recent years largely due to its inability to come up with new hit products as older drugs lost patent protection. A series of candidates failed in large clinical trials. One of its few remaining candidates is Arcoxia, a pain drug that is awaiting the Food and Drug Administration's decision this month. But the FDA is unlikely to approve Arcoxia quickly, analysts say, because it works similarly to Vioxx.

Meanwhile, Merck's biggest-selling drug, the cholesterol-fighter Zocor, is due to lose U.S. patent protection in 2006 and already is under pressure from the market leader, Pfizer's Lipitor.

risks with Vioxx are less than with naproxen, but the study shows increased cardiovascular risk.
• **February 2001:** FDA federal advisory panel concludes that Vioxx is safer on stomachs than rival drug Celebrex.
• **August 2001:** Cleveland Clinic study published in the Journal of the American Medical Association associates Vioxx with cardiovascular risks.
• **April 2002:** FDA changes Vioxx label to say the drug may protect against ulcers, but increase heart risks.
• **October 2003:** Merck-funded study finds patients taking Vioxx are at a 39% increased risk of heart attack within the first 90 days, compared with Celebrex.
• **August 2004:** HMO Kaiser Permanente reconsiders Vioxx for its member patients after an FDA study finds that patients who had taken more than 25 mg a day were 3.15 times as likely to have a heart problem.
• **September 2004:** FDA approves Vioxx to treat juvenile rheumatoid arthritis.
• **Sept. 30, 2004:** Merck announces a voluntary world-wide withdrawal of Vioxx.

Sources: Merck; WSJ research

Investors have been critical of Mr. Gilmartin's handling of the company's troubles. The announcement raises questions about whether he can survive until his scheduled retirement in 2006. Mr. Gilmartin said yesterday he doesn't plan to resign or change his longstanding policy against large mergers or takeovers.

"We were financially strong before this and we'll be financially strong after," Mr. Gilmartin said. He also pointed to several drugs for diseases such as diabetes and obesity that Merck is developing.

Vioxx's problems raise questions about the class of similar painkillers, called Cox-2 inhibitors. Aside from Vioxx, other approved Cox-2 inhibitors in the U.S. are Celebrex and Bextra, both Pfizer drugs. The drugs are heavily advertised and widely used, despite being more expensive than older drugs. Celebrex hasn't been linked to heart problems but some studies have suggested it fails to live up to its original promise of reducing side effects, in particular stomach bleeding.

Meanwhile, regulators are facing criticism for their handling of the questions around Vioxx, which emerged first in 2000. "Why did it take four years to get the definitive data?" asked Jerry Avorn, an associate professor at Harvard Medical School. "Why didn't the FDA demand the company mount the appropriate study?"

FDA officials note that the early hints of problems came largely from analyses of big databases of patients whose heart attacks might have been affected by many factors, rather than from controlled clinical trials like the new Merck information. "It's just not as easy to make firm regulatory decisions based on" such data, said Steven Galson, acting director of the FDA's Center

for Drug Evaluation and Research.

The decision to withdraw Vioxx was based on data from a big three-year clinical trial. The trial's main purpose was to determine whether Vioxx could prevent a recurrence of precancerous growths in the colon. If it could, that would open up a lucrative new market for the drug. But the trial also collected data on Vioxx's relationship to heart problems. John Jenkins, director of the FDA's office of new drugs, said the FDA pressed Merck to focus on cardiovascular safety in the trial's design. The study was a "very rigorous safety trial," he said. He added that FDA officials "feel confident, based on the data we had when we had it, we took the appropriate actions" with Vioxx.

Although the heart risk from Vioxx was the same as from a placebo through 18 months, people who took Vioxx for more than 18 months were twice as likely to have a heart attack or stroke during the study, Merck said. Lester M. Crawford, the acting FDA commissioner, said the risk that an individual patient would suffer a heart attack or stroke as a result of taking the drug is "very small." But he said patients taking any of the Cox-2 inhibitors or older painkillers for a long period should do so under a doctor's supervision.

Even prior to the withdrawal, Merck faced lawsuits from people who suffered heart attacks while taking Vioxx. Jay P. Mayesh, a partner with Kaye Scholer LLP in New York, who has defended drug makers in liability cases, predicted the recall will embolden plaintiffs. "It is going to be a king-size headache," Mr. Mayesh said. "Merck will be inundated with lawsuits." Merck said it will defend itself vigorously in the suits it faces.

The FDA approved Vioxx in 1999 for arthritis pain as well as other kinds of pain in adults. Later it was approved as a treatment for rheumatoid arthritis in adults and, just recently, for rheumatoid arthritis in children.

The long path to withdrawal of Vioxx began in 2000 when the New England Journal of Medicine published the results of a Merck trial called Vigor. It showed that patients taking the drug were four times as likely -- 0.4% to 0.1% -- to have a heart attack or stroke as patients taking naproxen.

In early 2001, at a meeting of an FDA advisory panel, Merck argued that the difference might reflect the protective effects of naproxen and not danger from its drug. The committee ended up recommending that the issue be noted on Vioxx's label, and members called for follow-up research to clear up the questions.

Steven E. Nissen, a cardiologist at the Cleveland Clinic, attended the meeting and was troubled by the data. Back at the clinic, he discussed his concerns with Eric Topol, chairman of cardiovascular medicine, and Debabrata Mukherjee, then a clinic fellow. They decided to take a closer look by examining data from several trials of patients who had taken Vioxx and other painkillers.

They published their findings in the Journal of the American Medical Association in August 2001, saying the "available data raise a cautionary flag about the risk of cardiovascular events" with Cox-2 inhibitors. Vioxx, they said, appeared especially risky. The authors called for more studies to look specifically at heart-safety issues, but Merck and other companies didn't start any.

Had such a trial been started, an answer probably would have been available within a year or two, said Harvard's Dr. Avorn. "That was millions of patients and billions of dollars ago," he said. Merck says its trials prior to Vioxx's approval hadn't turned up cardiovascular risk, and by 2001 it

was already conducting the study that would ultimately lead to Vioxx's withdrawal.

As concerns rose, however, Merck vigorously defended Vioxx. It attacked the Cleveland Clinic's data as inadequate. One study in which Merck researchers participated suggested that Vioxx was associated with a higher risk of heart attacks. It appeared last spring in Circulation, a journal published by the American Heart Association -- but without the name of a Merck scientist who participated. The company withdrew the employee's name from the list of authors because it disagreed with the study's conclusion.

The reason Vioxx might cause heart attacks isn't certain, but Cox-2 inhibitors suppress a protein responsible for the health of blood vessels and could promote clotting as a result. It's not clear why Vioxx produces a higher risk of heart attacks and Pfizer's Celebrex apparently does not, at least according to data so far.

In April 2002, the FDA, following up on the advisory panel's advice from the year before, approved new labeling for Vioxx that pointed out the association with higher heart-attack and stroke risk. In August of this year, the Cleveland Clinic's Dr. Topol wrote an editorial in the journal Lancet, saying it was time for the FDA "to have some teeth" on the issue and require a so-called black box label, the highest level of warning.

That turned out not to be necessary. Merck had been running a study testing whether Vioxx could prevent a recurrence of polyps, which are precursors to colon cancer.

Typically in clinical trials an independent body reviews data periodically to check for signs of unexpected benefits or dangers. Early on the evening of Sept. 23, an aide to Dr. Kim, the Merck research chief, got a call that the outside body wanted to halt the trial because of the cardiovascular risk to patients taking Vioxx, says Dr. Kim. Unlike other trials that compared Vioxx to competing drugs, this one compared Vioxx to a placebo. When the heart effects showed up, that effectively ended Merck's defense going back to 2000 that other drugs might protect the heart and blood vessels but Vioxx didn't damage them.

On Friday morning, Dr. Kim called Mr. Gilmartin, the Merck chief executive. "He told me that he wanted me to figure out what was the best thing to do in terms of patient safety," Dr. Kim says. Researchers worked through Sunday morning reviewing the numbers that had sparked the outside panel's call. The panel, they concluded, was correct.

Merck executives then consulted about two dozen outside experts in several medical fields. Some rheumatologists, who deal with pain complaints, advised Dr. Kim to keep Vioxx on the market and add a warning label. They said some patients respond particularly well to Vioxx and couldn't easily switch to other painkillers. Other doctors suggested Merck take the pill off the market completely. In the end, Dr. Kim followed this advice, concluding that the alternative drugs on the market were acceptable.

William G. Bowen, a Merck director since 1986 and president of the Andrew W. Mellon Foundation in New York, said management met all day Monday "to decide what they thought they should do."

Merck directors arrived in a downpour late Tuesday morning for a regularly scheduled board meeting at the company's New Jersey headquarters. Over a three-and-a-half-hour lunch session, Mr. Gilmartin and then Dr. Kim presented the research findings. Directors spent nearly 40

minutes discussing the study's statistical significance. But "the results were compelling," Mr. Bowen said. Everyone in the boardroom agreed that Merck should withdraw the drug.

Vioxx is the latest in a series of major drugs to be recalled from the market. Others include Baycol, a cholesterol-lowering drug, the diabetes drug Rezulin and the diet-pill combination fen-phen. In several cases, the FDA has faced criticism that it should have acted faster.

MERCK'S TOP SELLERS

Sales, in billions of dollars

Drug	Condition	2004*	2003	2002
Zocor	Cholesterol	$2.67	$5.01	$5.6
Fosamax	Osteoporosis	1.55	2.68	2.2
Cozaar/Hyzaar	Hypertension	1.35	2.49	2.2
Vioxx	Arthritis pain	1.31	2.55	2.5
Singulair	Asthma/seasonal allergies	1.27	2.01	1.5

*First half 2004. The 2003 and 2002 figures are for the full year.

Source: Merck

The FDA said it will now ask to see more long-term safety data for all of the drugs in Vioxx's class, but it hasn't decided the details of its request yet. The FDA's Dr. Galson said regulators "can't extrapolate data from one drug to another," but that other painkillers and Cox-2s "do not have this same incidence of heart attacks and strokes in clinical trials" so far.

Senate Finance Committee Chairman Charles Grassley, whose staff has been investigating the FDA's handling of safety issues, sent a letter asking for information about the agency's actions on Vioxx. "Once again, the FDA has remained on the sidelines while life-threatening issues threatened the American public," said the letter from the Iowa Republican.

One lawsuit against Merck, filed by relatives of a 37-year-old man who took Vioxx for a month and died from a heart attack at a car wash, is scheduled for trial in May. At a news conference, Merck's general counsel said the company has "substantial defenses" in current Vioxx cases.

Some lawyers say the withdrawal will insulate Merck from greater liability. "It was a good strategic move," said Kenneth M. Labbate, a lawyer with Ohrenstein & Brown LLP in New York who has defended drug companies in product-liability suits. "They know that the flood of litigation is coming one way or another, and what they're trying to do is put their best foot forward."

Even before yesterday's action, lawsuits against the drug maker had been mounting. Andy Birchfield, a lawyer for Beasley, Allen, Crow, Methvin, Portis & Miles, P.C., in Montgomery, Ala., already has filed 58 individual lawsuits against Merck on behalf of patients who have suffered heart attacks, strokes or other problems while taking Vioxx.

Mr. Birchfield said he believes he can prove to a jury that Merck kept selling a product it knew was dangerous. He expects his first case to come to trial as early as December.

After Vioxx, Merck needs new hits even more badly. It has stepped up deals with outside partners and this year has licensed marketing rights for a sleep drug and a diabetes drug now in large human trials. Last November, Merck called off development of two potential big sellers that came from its own labs, one for depression and the other for diabetes.

One of the few bright spots in Merck's labs is a vaccine against the human papilloma virus, a major cause of cervical cancer. It plans to submit an application to the FDA in the second half of 2005.

For the time being, Merck's loss is shaping up as Pfizer's gain. A Pfizer spokesman said the company is anticipating a surge in demand and is increasing the inventory of Celebrex and Bextra available to drug wholesalers. "All our long-term studies to date show a safe cardiovascular profile" for the Pfizer drugs, said Gail Cawkwell, a Pfizer medical director for Celebrex. But the Vioxx recall could make it harder for other Cox-2 drugs in development to get FDA approval, in particular Novartis AG's Prexige.

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