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January 15, 2008

Study Reveals Doubt on Drug for Cholesterol

By ALEX BERENSON

A clinical trial of a widely used cholesterol drug has raised questions both about the medicine's effectiveness and about the behavior of the pharmaceutical companies that conducted the study, cardiologists said Monday.

Merck and Schering-Plough, which make the drug, Zetia, and a pill that contains it, Vytorin, said Monday morning that Zetia had failed to benefit patients in a two-year trial that ended in April 2006.

Merck and Schering repeatedly missed their own deadlines for reporting the results, leading cardiologists around the world to wonder what the study would show. At the same time, millions of patients have continued taking Zetia and Vytorin.

The drug companies blamed the complexity of the data for the delay. Now, barely a month after news articles noted the delay and Congress pressured the companies to disclose the study's findings, the results are out.

In a press release, Merck and Schering said that not only did Zetia fail to slow the accumulation of fatty plaque in the arteries, it actually seemed to contribute to plaque formation — although by such a small amount that the finding could have been a result of chance.

Dr. Steven E. Nissen, the chairman of cardiology at the Cleveland Clinic, said the results were "shocking."

"This is as bad a result for the drug as anybody could have feared," said Dr. Nissen, a widely published researcher and senior consulting editor to the Journal of the American College of Cardiology. Millions of patients may be taking a drug that does not benefit them, raising their risk of heart attacks and exposing them to potential side effects, he said. Patients should not be given prescriptions for Zetia unless all other cholesterol drugs have failed, he said.

Both companies' shares fell Monday. Sales of the two drugs were $5 billion in 2007, and they are important contributors to Merck's and Schering's profits.

The House Energy and Commerce Committee, which is investigating the delay, said in a statement Monday that the negative results added to suspicions that the companies had deliberately sat on their findings from the study, which was known as Enhance.

"In light of today's results, which were released nearly two years after the Enhance trial ended, it is easy to conclude that Merck and Schering-Plough intentionally sought to delay the release of this data," Representative Bart Stupak, Democrat of Michigan, said in the statement. Mr. Stupak is chairman of the committee's Subcommittee on Oversight and Investigations.

Dr. Harlan M. Krumholz, a cardiologist at Yale, said drug companies had a responsibility to release all their trial findings, positive or negative, as quickly as possible — even if the results might hurt sales.

"People may have been on this drug without the ability to know that there was additional data that may have thrown into question its effectiveness," Dr. Krumholz said. "That's extremely

unfortunate, and that's an understatement."

Lee Davies, a spokesman for Schering, said the delay was unrelated to the negative findings and that the companies had not known the results until two weeks ago.

Dr. John Kastelein, a Dutch cardiologist who had conducted the Enhance trial for Merck and Schering, did not return calls or reply to an e-mail message seeking comment. Mr. Davies said that Dr. Kastelein would not comment until he formally presented the results at a cardiology conference in March.

In the trial, patients received either Zocor — an older cholesterol drug — or a combination of Zocor and Zetia, in the pill form known as Vytorin. About 60 percent of patients who take Zetia do so in the Vytorin form, which like Zetia is jointly marketed by Merck and Schering.

Worldwide, about one million prescriptions are written for Zetia and Vytorin each week, and about five million people are now taking the drugs worldwide.

The trial, called Enhance, covered 720 patients and lasted two years. While it was relatively small, cardiologists have been were eager to see its results because they have far less data on Zetia than on other cholesterol-lowering medicines.

Statins like Zocor and Lipitor have been shown to lower cholesterol by 35 to 60 percent in most patients and have also been proved to reduce heart attacks. Zetia, which works by a different mechanism, reduces cholesterol 15 to 20 percent, but it has never been proved to reduce heart attacks.

The Enhance trial was meant to prove that Vytorin's combination of Zetia and Zocor would reduce the growth of fatty plaque in the arteries more than Zocor alone. Instead, the plaque

actually grew almost twice as fast in patients taking the combination.

Reducing plaque growth is crucial, because plaque formation — known as atherosclerosis — can lead to the blockages and blood clots that cause heart attacks and strokes, said Dr. Howard N. Hodis, a cardiologist at the University of Southern California. That is why the trial's finding is worrisome, Dr. Hodis said.

"Clearly, progression of atherosclerosis is the only way you get events," Dr. Hodis said. "If you don't treat progression, then you get events."

The results of the trial require further investigation, Dr. Hodis said. "That just can't be ignored."

Dr. Michael Davidson, a cardiologist in Chicago who has conducted clinical trials of Zetia for Merck and Schering, said the Enhance results did not necessarily mean the drug did not work. Many of the patients in the trial may have been on statins for many years before the trial began, so adding Zetia may have had only marginal benefits compared with its use in a population not as extensively treated for cholesterol, he said.

Still, he said, patients should generally receive a statin before getting Zetia.

Beyond the Enhance trials, Merck and Schering recently began two large clinical trials intended to test whether the combination of Zetia and statin drugs actually reduces heart attacks and strokes when compared with statins alone. But the data from those trials will not be available until at least 2011.

Merck and Schering share profits from their joint marketing of Zetia and Vytorin. The drugs

are important contributors to both companies' profits, but more so to Schering, which is smaller and less profitable than Merck. Analysts estimate that about 70 percent of Schering's earnings depend on Zetia and Vytorin .

Merrill Lynch on Monday reduced its rating on Schering's stock from buy to neutral, warning that some doctors might move away from Zetia. Schering's share price fell 8 percent , while Merck's dipped 1.3 percent.

Because Zetia reduces cholesterol in a different way from statins like Lipitor and Zocor, doctors often prescribe it as an additional therapy for patients whose cholesterol remains high even after they are already taking statins.

But even before Zetia was introduced in 2002, some cardiologists argued that statins have positive cardiovascular effects that go beyond their ability to reduce cholesterol, and that Zetia lacks those effects.

The Enhance trial covered patients who have a gene that causes them to produce high levels of low-density lipoprotein cholesterol, commonly called LDL or bad cholesterol. Patients in the trial had LDL levels of about 320 milligrams per deciliter at the beginning of the trial, about three times the level cardiologists deem acceptable.

Over the two years of the trial, patients who took Zocor alone reduced their LDL by 41 percent on average, while patients who took Vytorin reduced their cholesterol by 58 percent. Yet despite the larger cholesterol reduction, patients taking Vytorin actually had more growth of fatty plaque in their carotid arteries than those on Zocor.

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