Data About Zetia Risks Was Not Fully Revealed

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New evidence shows that the drug makers Merck and Schering-Plough have conducted several studies of their popular cholesterol medicine Zetia that raise questions about its risks to the liver, but the companies have never published those results.

Partial results of the studies, alluded to in documents on the Food and Drug Administration's Web site, raise questions about whether Zetia can cause liver damage when used long term with other cholesterol drugs called statins.

Most of the millions of people who use Zetia take it along with a statin like Lipitor, Crestor or Zocor. Or they take it in a single pill, Vytorin, that combines Zetia with Zocor.

The discovery of the unpublished research comes as Merck and Schering are already under criticism for not yet releasing data from an important Zetia study, called Enhance, that they completed early last year.

The Enhance data may also contain important information about Zetia's liver risks. At least some patients were dropped from the Enhance study after testing revealed that they had elevated liver enzymes, a Schering-Plough spokesman confirmed this week.

But a full report on that trial, including the number of patients who had liver problems, will not be available until March.

Doctors say that by failing to disclose promptly all their research, Merck and Schering-Plough may be leaving the public with a misleadingly favorable view of Zetia's safety and benefits.

"You don't want to have data missing," said Dr. Bruce Psaty, a professor of medicine and epidemiology at the University of Washington. "When there have been adverse effects, when the benefits don't look impressive, those are the trials that historically don't make it to press."

A Schering executive, when asked by a reporter about the unpublished studies, confirmed their existence. But the executive, Dr. Robert J. Spiegel, said the companies had not considered the studies scientifically important enough to publish their findings. Some may eventually be published, he said.

“We’re pretty comfortable that people don’t have trouble tolerating Zetia,” said Dr. Spiegel, the chief medical officer of the Schering-Plough Research Institute, Kenilworth, N.J.

Schering also said that the F.D.A. had reviewed the data from the unpublished studies and had approved Zetia for use alongside statins. But experts on drug safety say that the agency has been slow to issue warnings about many widely used drugs that have turned out to carry serious risks, including the painkiller Vioxx, the diabetes medicine Avandia and the anti-psychotic drug Zyprexa.

Even doctors critical of Zetia generally say it is safe for most patients. But before the drug was approved in 2002, one F.D.A. reviewer said it should not be cleared for use with statins because the combination had caused liver damage in animals. And in the last two years, scattered case reports of severe liver damage in patients taking Zetia in combination with statins have appeared in medical journals.

In the United States, the product label for Zetia contains only mild warnings about the drug’s potential for liver damage.

But in Australia and Canada, regulators have been more cautious. Since 2005, they have issued a series of warnings about Zetia’s potential to cause hepatitis, pancreatitis and depression — warnings that have largely gone unnoticed in the United States.

All drugs have potential risks and side effects, of course, and doctors and patients must weigh those against a drug’s medical benefits. But in the case of Zetia, despite its widespread use, there is no evidence proving that Zetia can reduce heart attacks and strokes, as cholesterol drugs are meant to do. There is extensive medical evidence showing that Lipitor and other statins provide such protection.

The unpublished Zetia studies, devised as safety tests, would not prove the drug’s effectiveness. But they would give the public more information about Zetia’s potential risks. All the unpublished studies covered periods at least one year in length and were intended to show whether long-term use of Zetia might pose dangers that short-term use did not.

Most of the studies about Zetia in which Merck and Schering have published the results covered periods of only 12 weeks — not enough time for liver problems to develop in most patients.

The unpublished studies, conducted from 2000 to 2003 according to the F.D.A. documents, were not listed on the industry Web sites where companies are supposed to register the results of all drug trials that were ongoing after October 2002. The New York Times discovered references to the studies in briefing papers on the F.D.A. Web site.

“We keep telling people we want to practice evidence-based medicine, and what we keep finding out is that much of the evidence is obscured,” said Dr. Harlan Krumholz, a cardiologist at Yale, when told about the previously undisclosed studies. “There is important evidence, but it’s not in public view. It’s hidden from investigators.”

Schering and Merck — which are on track to earn $5 billion this year from sales of Zetia — had already been criticized for not promptly releasing results of the Enhance trial, which was completed in April 2006. Under pressure from Congress and prominent cardiologists, the companies said recently that they would release the full results of the Enhance trial by March.

In response to questions from The Times, the Schering spokesman, Lee Davies, disclosed this week that some patients in the Enhance trial had been dropped from it after tests showed that they had elevated liver enzymes — a potential sign of organ damage. But Mr. Davies said he could not disclose how many, and said the companies did not even know if the patients who had been dropped were taking Zetia and a statin, or just a statin. The delay in releasing the Enhance trial data is unrelated to the patients who were discontinued, Mr. Davies said.

The Enhance data are expected to provide the clearest picture yet of Zetia's long-term affects. But the F.D.A.'s documents show that Merck and Schering conducted several other long-term trials of Zetia without releasing their findings.

Together those studies cover several thousand patients who took Zetia along with statins for one to two years. The statins include Lipitor and Crestor, as well as Zocor, which is usually prescribed generically as simvastatin and is the statin used in the Vytorin pill. Doctors often add Zetia to a low dosage of a statin, because Zetia reduces cholesterol in a different way than the statins do and leads to deeper overall cholesterol reductions.

One open question is whether Zetia's method of lowering cholesterol provides the same medical benefits as fighting cholesterol with a higher-dose statin by itself. Last year, Merck and Schering began a separate study — a 10,000-patient clinical trial to prove that Zetia's ability to lower cholesterol will translate into fewer heart attacks and strokes in patients. But data from that trial will not be available until at least 2011.

In the meantime, some doctors say, they must essentially take on faith that Zetia's cholesterol-lowering ability will translate into real-world benefits and that its long-term use with statins does not have major risks.

Dr. Eric J. Topol, a cardiologist and director of the Scripps Translational Science Institute in La Jolla, Calif., said that he had asked Merck and Schering more than four years ago to conduct a large, long-term trial to prove that Zetia could reduce heart attacks and strokes. But the companies had little interest, he said.

"They looked at me like I was an alien," Dr. Topol said.

Two months ago, President Bush signed a new law intended to strengthen penalties for companies that do not release information promptly. And in 2004, the drug industry promised to improve disclosure of research results.

But the new law applies only to new trials, meaning the unpublished Zetia trials are not covered by those new rules and guidelines.

The F.D.A. has reviewed the unpublished studies, according to the agency's briefing papers.

The companies' own published studies have generally played down the risk of liver problems. But Dr. Mark Stolk, a gastroenterologist in the Netherlands, last year reported two cases of patients who had developed hepatitis, a liver disease, after taking Zetia alongside Lipitor. One of the patients has since died, Dr. Stolk said in an interview last month. While Zetia is safe for most patients, doctors should carefully monitor patients for liver damage, he said.

"I think other cases will emerge," he said.

When the F.D.A. approved Zetia in 2002, it relied on trials that covered only 3,900 patients and lasted no more than 12 weeks. Still, the data from even those trials contained signals that Zetia might be dangerous in some patients when it is taken alongside statins, as it usually is.

In those trials, 11 times as many people who took Zetia along with a statin subsequently had serious health problems, compared with those who took a statin alone. Nearly all the serious problems were liver-related. Still the F.D.A. regarded the risks as relatively minor and approved Zetia without asking the companies to conduct longer trials.

The agency did not respond to requests for comment.

All drugs have risks, of course. Doctors who prescribe Zetia say that while they would prefer to see long-term trial data, they are comfortable using it because decades of evidence demonstrated that lowering LDL, or so-called bad cholesterol, is good for patients.

But Dr. Beatrice A. Golomb, an associate professor at the University of California, San Diego, said doctors have lost sight of the purpose of prescribing drugs like Zetia.

The goal of prescribing cholesterol-lowering drugs is not reducing cholesterol, Dr. Golomb said. It is reducing the number of deaths and heart attacks in patients, he said. And without data to prove that Zetia actually reduces heart attacks, doctors cannot be sure they are helping patients when they prescribe the drug, she said.