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Cholesterol Drug Zetia May Cause Serious Liver Injury Including Hepatitis And Liver Failure

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POSTED: Friday, December 21, 2007

FROM BLOG: [Drug Injury Watch](#) - Prescription Drug Side Effects News and Information from Attorney Tom Lamb

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Health Canada First Raised This Zetia Safety Issue In February 2005; News Reporter Discovers In December 2007 That Information Known By Merck and Schering-Plough About These Zetia Side Effects May Have Been Withheld (Posted by Tom Lamb at [DrugInjuryWatch.com](#))

Back on February 1, 2005 Health Canada posted on its web site a so-called "[Dear Doctor](#)" letter about Zetia (ezetimibe) -- called Ezetrol in Canada -- from Merck Frosst / Schering Pharmaceuticals that was intended to draw attention to some serious side effects associated with Zetia. That 2005 Dear Doctor letter included the following:

The Warnings, Precautions, and Adverse Events sections are being updated to reflect the occurrence of the following adverse events in patients taking Ezetrol® (ezetimibe) alone or in combination with a statin:

- myalgia;
- rhabdomyolysis;
- hepatitis;
- acute pancreatitis;
- thrombocytopenia; and
- suspected interaction between Ezetrol® (ezetimibe) and warfarin

In the U.S., however, Merck and Schering-Plough -- the drug companies responsible for Zetia, here -- chose not to send any corresponding Dear Doctor letter to American health care professionals, nor did the FDA mandate that they do so.

Returning to [this 2005 Dear Doctor letter about Zetia](#), here is what was said about liver injuries to patients using Zetia and a statin drug (such as Zocor, Lipitor, Crestor, Lescol, Mevacor, or Pravachol):

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Adverse hepatic events:

Elevations of liver transaminases and cases of hepatitis have been reported in patients treated with [Zetia]. Liver function monitoring is recommended when therapy with [Zetia] is initiated in patients treated or about to begin treatment with a statin.

Health care professionals should be aware that the use of [Zetia] in combination with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations of liver transaminases.

In the two years since this 2005 Dear Doctor letter about Zetia was sent by the Merck and Schering group in Canada there have been some case reports of serious liver injury in patients using Zetia and statins -- but for the most part Zetia-induced liver injury had been off-the-radar for most drug safety observers.

Now we have some idea about why, perhaps, Zetia-induced liver injury side effects were not more widely known.

In a December 21, 2007 article, "[Data About Zetia Risks Was Not Fully Revealed](#)", *New York Times (NYT)* reporter Alex Berenson broke the story that Merck and Schering-Plough had conducted several studies of Zetia which, in fact, raised the possibility that Zetia can cause liver damage when used long-term with other statins - - but these drug companies decided not to publish the results of those Zetia studies.

In preparing for his December 2007 Zetia article, the *Times'* reporter Alex Berenson spoke to a drug company representative and some medical doctors about this reporter's discovery of unpublished research about Zetia and liver-related side effects.

We'll start with comments from two doctors who spoke with Mr. Berenson about this emerging drug safety issue:

"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."...

"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."

On the other side of things, the Schering-Plough representative had this to say :

A Schering executive, when asked by a reporter about the unpublished [Zetia] studies, confirmed their existence. But the executive, **Dr. Robert J. Spiegel, said the companies had not considered the [Zetia] 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. (Emphasis added.)

In his December 2007 *NYT* article Mr. Berenson provides some reasons, however, why doctors and patients may not want to go along with this "reassurance" from Schering's Dr. Spiegel:

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....

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....

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.

What does the FDA have to say about this news reporter's discovery of unpublished studies suggesting that Zetia can cause serious liver injury when taken with statins? Mr. Berenson tells us: "The agency did not respond to requests for comment."

To be sure, we will be reporting further developments as more is learned about the safety of Zetia -- one way or the other.

P.S. Given how *NYT* reporter Alex Berenson discovered that Merck and Schering-Plough failed to publish some studies about Zetia and liver damage, Ed Silverman timely posted "[How To Find Documents On The FDA Site](#)" on his Pharnalot blog:

This cheat sheet should help you find briefing documents - the reams of supporting paperwork submitted by a drugmaker when seeking FDA approval for its med. It was compiled by a professor and students at the Lake Erie College of Osteopathic Medicine's School of Pharmacy and recently published in the letters section of *The Annals of Pharmacotherapy*.

Thanks Ed for this insight about how emerging drug-safety issues (like the *NYT* Zetia story) can be found and exposed. (12/21/07)

P.S. Dr. Aubrey Blumsohn, over at the *Scientific Misconduct Blog*, gives us his strongly worded opinion about the position asserted by Schering's medical director in the *NY Times* story about Zetia and Vytorin, which I have bolded above.

In his post, "[More problems with Ezetimibe \(Zetia, Vytorin\): Let there be light](#)", Dr. Blumsohn writes:

... Dr. Spiegel, it's not your decision. When patients might die it's always "scientifically important".

In addition, Dr. Blumsohn provides links to some other articles about this emerging Zetia study data controversy. (12/23/07)

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