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From the Los Angeles Times

Concerns about diabetes drug Avandia aren't new

Public Citizen releases a 2002 FDA memo warning that the pill may spark serious heart problems. Actos is also at issue.

By Ricardo Alonso-Zaldivar
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WASHINGTON — Federal investigators warned nearly five years ago that the diabetes drug Avandia might be causing heart failure, according to an internal government memo released Tuesday by a consumer group.

Investigators also raised concerns about Actos, a similar drug used to treat Type 2 diabetes.

Separately, in fast-moving developments in the latest drug safety investigation, a senior Republican senator said Tuesday he had learned that the Food and Drug Administration's safety office had recommended the strongest possible warning for Avandia — only to be overruled.

"The FDA didn't take that advice," said Sen. Charles E. Grassley (R-Iowa), a critic of the agency. "Instead, the warning about congestive heart failure risks with this drug is currently buried."

FDA spokeswoman Julie Zawisza responded that debate and disagreement were not unusual within the agency, "particularly when the science is unclear, complex or emerging."

"We do not have sufficient understanding of the data at this time to make a regulatory decision," she said.

The FDA issued a safety alert about Avandia on Monday after a study in the *New England Journal of Medicine* linked the medication to increased risk of heart attacks and death from cardiac disease. The alert underscored less prominent warnings of heart risks in prescribing literature primarily intended for doctors.

But a memo from FDA drug safety reviewers — dated July 16, 2002 — indicates there were significant concerns much earlier within the agency about Avandia and Actos.

Released by the watchdog group Public Citizen, the memo analyzed 47 early reports to the FDA of patients who went into heart failure and had to be hospitalized while taking one of the drugs. Congestive heart failure, or CHF, is a life-threatening condition that comes about when the heart is unable to pump enough blood to the rest of the body.

"This case series strongly supports the hypothesis that [these drugs], as a class, may be associated with CHF in diabetics," the memo said. The safety reviewers went on to recommend changes in prescribing information to alert doctors to their findings, as well as follow-up studies to definitively resolve suspicions.

"With this kind of evidence in 2002, there should have been a sharp decrease in the prescribing of these drugs," said Dr. Sidney Wolfe, director of Public Citizen's Health Research Group. "Instead, just the opposite happened."

The group, founded by activist Ralph Nader, obtained the memo under the federal Freedom of Information Act.

Zawisza, the FDA spokeswoman, said the prescribing literature for Avandia and Actos has been updated repeatedly to include warnings about the risks of heart failure, using "much better information" than was contained in the 2002 memo.

A spokeswoman for GlaxoSmithKline, which makes Avandia, said the company had changed the drug's prescribing information as early as 2000 to warn doctors of heart failure risks.

"All the concerns raised in the memo had already been addressed," Alice Hunt said.

Takeda Pharmaceutical Co., the Japanese manufacturer of Actos, could not be immediately reached.

Both drugs, which are widely prescribed for the treatment of adult-onset diabetes, are believed to work by breaking down the body's resistance to insulin. However, even before they were approved in 1999, Avandia and Actos were also known to cause fluid retention — a major risk factor for congestive heart failure. Nonetheless, they were seen as a safer alternative to Rezulin, a similar medication withdrawn after it was linked to liver failure.

Wolfe said the case reports from the FDA database should have been included in the warnings to doctors. And the FDA should have considered stronger warnings that the drugs be used only as a last resort — at least until the safety issues could be resolved.

Three congressional panels are investigating the FDA's handling of Avandia — including the Senate Finance Committee, where Grassley is the ranking Republican. The FDA is conducting its own review, which will probably encompass both drugs, but it could take several months.

About 6 million Americans have taken Avandia, according to GlaxoSmithKline.

The 2002 FDA memo analyzed 25 cases of heart failure in Avandia patients and an additional 22 cases in patients who were taking Actos. In 26 of the cases, the patients had not previously been diagnosed with heart failure — a signal the safety reviewers found worrisome. One patient taking Avandia died.

In the memo, the safety reviewers said the symptoms of fluid retention appeared to build up slowly over a period of several months in an "insidious" manner that might not be easy for doctors to detect. And they expressed concern that such risks were not "clearly defined" in the prescribing literature available to doctors.

Since that time, the number of case reports of serious problems has grown significantly, Wolfe said. The FDA now has 803 reports of patients who had to be hospitalized for heart failure while taking the diabetes drugs — 415 for Avandia and 388 for Actos.

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