



## **The Final Word on Avandia: Diabetes Drug Should Stay Despite Heart Risks**

### **FDA panel says Avandia offers benefits to people with type 2 disease, but.....**

The widely prescribed type 2 diabetes drug Avandia should remain on the market, despite studies that suggest it could increase the risk of heart attacks, U.S. health advisers said Monday.

The U.S. Food and Drug Administration advisory panel voted 22-1 to keep the drug on the market, although it recommended Avandia should carry new safety warnings. That vote was preceded by another vote, 20-3, in which panel members agreed that available data does show Avandia increases heart risks.

"The committee felt, almost uniformly, that there is a risk to some patients," said Dr. Clifford Rosen, the acting committee chairman from the Maine Center for Osteoporosis, St. Joseph Hospital, in Bangor.

"There was some increased risk of cardiac events to some patients. The signal for increased risk was there, with some qualifications," he told reporters at a teleconference.

Patients at risk include those with congestive heart failure, heart disease or patients using insulin, Rosen said, adding, "There are clear-cut reasons not to prescribe this drug to certain patients."

But the decision to keep the drug on the market, according to an FDA official, came about because the committee wasn't convinced that the data presented about the risk was conclusive. "If we have a clear answer, we don't take this to an advisory committee," Dr. Robert Meyer, the director of the FDA's Office of Evaluation II, Center for Drug Evaluation and Research, told reporters.

Dr. Gerald Dal Pan, director of the FDA's Office of Surveillance and Epidemiology, said, "We will go back and formulate what we think should be on the label." Panelists' suggestions included a black box warning or other warning for heart attack, but there was no consensus on how the label should be changed, he said. The FDA had previously asked the drug's manufacturer, GlaxoSmithKline, to add a black box warning about heart failure.

While the FDA isn't bound to follow the recommendations of its advisory panels, it typically does so. Concerns about Avandia (rosiglitazone), part of a class of drugs for diabetes called thiazolidinediones, are based on a meta-analysis of published studies that suggested the drug increases the risk of heart attack by 43 percent.

That finding was first published May 21 in the *New England Journal of Medicine*, in a paper co-authored by Dr. Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic and

one of the earliest critics of the arthritis drug Vioxx, which was withdrawn from the market in 2004 due to heart attack concerns.

Dr. Larry Deeb, president for medicine and science at the American Diabetes Association, said before Monday's vote that he believes Avandia should continue to be available to diabetics because the increased risk of heart attack has not been proven conclusively.

"A decision to do something should not be based on a nebulous risk," Deeb said. "There probably should be a warning on the box, because there is enough concern." Deeb believes the FDA should call for a study to thoroughly review any heart risks associated with the drug's use. "It's premature to withdraw the drug. I am anxious about pulling [a drug] that has done some good off the market based on a meta-analysis," he added.

Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, who has previously spoken out against Avandia, was among the speakers at the hearing. "Does the overall risk-benefit profile of Avandia support its continued marketing in the United States? The answer is clearly no," he said in a prepared statement.

According to Wolfe's prepared testimony, FDA adverse-reaction reports filed since Avandia hit the market in 1999 have shown the drug had a 15.2 times higher adjusted rate of heart failure than did the older diabetes drug Glucotrol. The adjusted rate of liver toxicity with Avandia was 9.5 times higher, and 14.8 times higher for liver failure, he said.

"There is no evidence of any uniquely beneficial clinical outcome for Avandia and growing evidence of unique risks in multiple organ systems," Wolfe said. "If Avandia were up for approval today, based on what is now known, it would be summarily rejected. There should not be a double standard for removing it from the market."

For its part, Avandia's maker, GlaxoSmithKline, insisted before the meeting that the drug does not increase the risk of heart attack. "We don't believe that a warning about heart attack should be on the label," said Dr. Andy Zambanini, director of clinical development at GlaxoSmithKline.

"Avandia is one of the most studied medicines in the diabetes field," Zambanini said. "We have looked at all the available data both from short-term trials, long-term trials and real-world data, in terms of epidemiology. There is really no evidence of an increase in cardiovascular death with Avandia. And when you look at Avandia and compare it with all the other similar agents, there really is no difference in heart attack risk."

One of the studies that GlaxoSmithKline is relying on to make its case is the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial. The study, sponsored by Glaxo, was specifically designed to determine the risks for heart attack from Avandia.

Dr. David Graham, associate director for science and medicine in the FDA's Office of Surveillance and Epidemiology and an Avandia critic, disagreed with Glaxo's interpretation of the RECORD study. In a report submitted by the FDA to the advisory panel before the hearing, Graham concluded:

"RECORD does not now, nor will it at completion, provide meaningful evidence to demonstrate with any degree of certainty that RSG [Avandia] does not increase the risk of acute myocardial infarction

[heart attack] or sudden death, or the APTC outcome. The biased design of RECORD renders it useless as an objective measure of Avandia's cardiovascular safety." Zambanini countered by saying that the RECORD study has seen very few cardiac deaths. "To say that this study is of no value isn't true," he said.

During Monday's testimony, Graham was supported by his boss, Dal Pan, who said the risks posed by Avandia outweighed the benefits. But another agency official, Dr. Robert Meyer, head of the FDA office that reviews new diabetes drugs, urged panel members to keep an open mind about Avandia, the AP reported. "It is important that the committee understand there is a fundamental disagreement within (the FDA's drugs office) on the scientific conclusions that should be drawn," Meyer said. That rift revealed a division between FDA officials responsible for approving new medicines and those who monitor their safety once on the market, the AP said.

Currently, there is a warning on Avandia's label that it increases the risk of another cardiovascular problem called congestive heart failure, a chronic condition caused by the heart's failure to pump normally, allowing fluid to build up in the body. In May, the FDA said it wanted a stronger warning about the risk of heart failure on Avandia's label. Glaxo is "still in negotiation with the FDA about a new warning label on heart failure and we expect to release that information soon," Zambanini said.

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