

Company Disputes Results

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data are borne out by further analysis and the results of larger controlled trials," the authors wrote.

In its initial response to the current study, the manufacturer of rosiglitazone, GlaxoSmithKline, issued a statement saying the company "strongly disagrees with the conclusions ... which are based on incomplete evidence and a methodology that the author admits has significant limitations."

"We know that there were some weaknesses to our analysis, but we think that it will stand up as a valid reflection of the risk of the drug," Dr. Nissen, chairman of the department of cardiovascular medicine at the clinic, replied in an interview.

The meta-analysis involved 5 studies that originally were submitted to the Food and Drug Administration for an advisory board hearing on the drug's approval, 35 trials initially identified in GlaxoSmithKline's clinical-trial registry (9 published and 26 unpublished), and 2 large, recently published trials (DREAM—Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication and ADOPT—A Diabetes Outcome Progression Trial). All of these trials included a total of 15,560 patients who were randomized to receive regimens that included rosiglitazone and 12,283 who were assigned to control groups that took an active comparator or placebo.

The small number of MIs (86 with rosiglitazone and 72 with control) and deaths from cardiovascular causes (39 with rosiglitazone and 22 with control) make the results susceptible to small changes in the classification of events. The lack of a

standard method for identifying or validating outcomes in the trials might have caused these events to be missed or misclassified, Dr. Bruce M. Psaty of the University of Washington, Seattle, and Dr. Curt D. Furberg of Wake Forest University, Winston-Salem, N.C., wrote in an accompanying editorial (N. Engl. J. Med. 2007 [Epub doi:10.1056/NEJMoa072761]).

Because the investigators had access to only trial-level data and not patient-level data, they could not determine the outcome of the composite of death or myocardial infarction. Time-to-event data for cardiovascular events were not available for these trials, so hazard ratios could not be calculated.

In a May teleconference, Dr. Robert J. Meyer of the Food and Drug Administration's Center for Drug Evaluation and Research said that an unpublished reanalysis of the DREAM trial provides "contradictory evidence about the risk in patients treated with Avandia," compared with the current meta-analysis.

In a letter published online in *The Lancet* after the company's initial statement was released, Dr. Ronald L. Krall, chief medical officer for GlaxoSmithKline, acknowledges internal company meta-analyses from 2005 and 2006 with "hazard ratios in the same direction" as those found in the meta-analysis by Dr. Nissen and Ms. Wolski. However, he added, "All these results are highly dependent on the methods used and the studies included, given the small number of events reported." He also suggested that meta-analyses might be less revealing than

the results of individual trials (doi:10.1016/S0140-6736[07]60824-1).

Since the publication of ADOPT (N. Engl. J. Med. 2006;355:2427-43), GlaxoSmithKline's further analysis of all major cardiovascular events found "such events were rare in this population and that all treatments were comparable," wrote Dr. Krall. Similarly, after the publication of DREAM (Lancet 2006;368:1096-105), the company's further analysis "found that similar numbers of patients on rosiglitazone, ramipril, and placebo had cardiovascular events. The increased numbers of events in the rosiglitazone plus ramipril group of the study is currently unexplained," he wrote.

Dr. Nissen said in an interview that he would not comment on Dr. Krall's letter because the further analyses that Dr. Krall referred to were unpublished and have not been peer reviewed. Dr. Nissen also noted that "It's an unusual way to publish results in a letter to the editor from the company's chief medical officer as opposed to a scientific publication."

Dr. Meyer said the FDA does not know if the potential increased risk of MI or heart-related death extends to other thiazolidinedione drugs, such as pioglitazone (Actos). He emphasized that doctors should talk with their patients who have underlying heart disease or are at risk for an MI about their individual treatment options and what these studies mean.

Dr. Meyer said that the FDA received a meta-analysis from GlaxoSmithKline in August 2006 that included another set of 42 randomized, controlled trials (many of which are likely the same as those in the current study). The FDA is reanalyzing this study because of some issues with the way in which the company did its analysis. That

meta-analysis also indicated an increased risk of MI and heart-related adverse events.

The most recent labeling change for rosiglitazone included a new warning about a potential increase in heart attacks and heart-related chest pain in some individuals using rosiglitazone. This new warning was based on the result of a controlled clinical trial in patients with existing heart failure, according to the FDA.

Dr. Hellman, who also is clinical professor of medicine at the University of Missouri, Kansas City, said the findings "highlight the fact that there's something we don't know yet about the glitazones." He added, "Now we need to be careful in the analysis; it's possible that these results could have been due to chance, but it's also possible that they may indicate a problem with certain groups of patients that has not yet been uncovered."

The glitazones probably affect more than 100 genes in the human body, noted Dr. Hellman. "When an agent is so active at the gene level, postmarketing studies need to address the issue of special populations."

In their editorial, Dr. Psaty and Dr. Furberg said that, "in view of the potential cardiovascular risks and in the absence of evidence of other health advantages, except for laboratory measures of glycemic control, the rationale for prescribing rosiglitazone at this time is unclear. Unless new data provide a different picture of the risk-benefit profile, regulatory action by the FDA is now warranted."

"I think the FDA needs to begin to think more clearly about these kinds of risky situations and act earlier," Dr. Nissen said. ■

Montreal Bureau Chief Kate Johnson contributed to this report.

Lots of Finger Pointing at Congressional Hearing on Avandia

BY JOYCE FRIEDEN
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WASHINGTON — A June 6 congressional hearing on the approval process and oversight of rosiglitazone found members of Congress pointing accusatory fingers at almost everyone who testified, including officials from the Food and Drug Administration, the company producing the drug, and the scientist who published a study expressing concerns about the drug's cardiovascular effects.

Rep. Henry Waxman (D-Calif.), chairman of the House Committee on Oversight and Government Reform, set the tone for the hearing in his opening statement. "It is not Congress' role to adjudicate these medical issues," he declared. "But it is our role to ensure that the Food and Drug Administration is taking these concerns seriously and providing doctors and patients with the guidance they need to make informed decisions."

Committee member Darryl Issa (R-Calif.) fired back, questioning the need for the hearing. "I'm concerned that we not tread too closely toward the hypocrisy this hearing begins to look like," he said. "Politicizing science is what we could be doing here today."

The hearing was held 3 weeks after Dr. Steven Nissen of the Cleveland Clinic and his colleague, Kathy Wolski, published a meta-analysis in the online edition of the *New England Journal of Medicine* suggesting that type 2 diabetes patients taking rosiglitazone had a 43% higher risk of myocardial infarction (MI) compared with patients on other drug treatments. (See story, p. 1.)

The day before the congressional hearing, the journal published interim results from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, which looked at hospitalization



Dr. Steven Nissen of the Cleveland Clinic testifies at a congressional hearing on the oversight of Avandia.

or death from cardiovascular causes. The authors concluded that "the data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction" (Epub doi: 10.1056/NEJMoa073394). Three accompanying editorials all suggested that such a risk warranted careful consideration of the drug's use.

At the hearing, Rep. Waxman questioned FDA Commissioner Dr. Andrew von Eschenbach about why the agency did not take seriously the concerns of one of its own medical reviewers at the time the drug was approved.

Although the drug achieved the purpose of lowering blood sugar in patients with type 2 diabetes, "the increase in body weight and undesirable effects on serum lipids is cause for concern . . . It cannot be assumed that treatment with rosiglitazone will decrease the risk" of heart disease,

according to the FDA's medical review dated April 1999. The reviewer recommended that a postmarketing study be done to address those concerns.

Dr. von Eschenbach defended the agency's actions, noting that the FDA has been monitoring cardiovascular adverse events, including edema and heart failure, since rosiglitazone was approved. He also said that rosiglitazone's label was updated in April 2006 to include new warnings about a potential increase in MIs in heart failure patients.

Dr. von Eschenbach noted that the agency was still analyzing follow-up data that it has received, and that it has scheduled an advisory committee meeting for July 30 to discuss whether additional action needs to be taken.

Rep. Issa admonished Dr. Nissen for his failure to share his findings with the FDA prior to publication. "You didn't even give them the benefit of the doubt," Rep. Issa said.

Dr. Nissen responded that the FDA had access to all the data he had and added that submitting findings for peer review and publication was standard scientific practice.

Dr. John Buse, president-elect of the American Diabetes Association and director of the Diabetes Care Center at the University of North Carolina, Chapel Hill, testified that he first raised the issue of rosiglitazone's cardiovascular side effects in 1999. Dr. Buse said that officials at SmithKline Beecham—the predecessor to GlaxoSmithKline—then tried to intimidate him, implying that he could be held personally liable for the \$4-billion drop in the company's value that occurred after his concerns became widely known.

In response to a question from Rep. Waxman about the "shocking" way Dr. Buse was treated, Moncef Slaoui, Ph.D., chairman of research and development at GSK, said that "there was a lot of passion on his side and on the side of the [company's] scientists" regarding the issue of rosiglitazone's safety. "We regret that Dr. Buse felt pressured." ■