US: FDA accused of negligence over diabetes drug

Joanne Laurier
26 May 2007

The US federal Food and Drug Administration (FDA) has come under sharp criticism this week for its inaction over the diabetes drug Avandia. The FDA apparently failed to implement the recommendation made several months ago by its own experts that the widely prescribed drug should carry the strongest possible warning on its label.

In a floor statement placed in the Senate record on Thursday, Senator Charles Grassley, Republican of Iowa, said that some FDA staff members had advised that the prescribing information for the medicine should include a caution framed by a black box, the most serious type of alert.

On May 21, the prestigious *New England Journal of Medicine* (*NEJM*) published a report linking Avandia, made by the British company GlaxoSmithKline, to an increased risk of heart attack and heart-related death.

Grassley complained that top officials in the FDA said they wanted to postpone making any decisions about the drug until the completion of an ongoing study slated to continue for at least two more years. The FDA's own evaluation of Avandia suggests that as many as 60,000 to 100,000 heart attacks may be linked to its use since it came on the market eight years ago. Grassley contends that the number of heart attacks possibly linked to the drug could be as high as 20 a day.

NEJM reported on the results of a study on the blockbuster pharmaceutical used to treat type 2, or adult-onset, diabetes by the Cleveland Clinic's Steven Nissen and Kathy Wolski. The analysis, which pulled together a review of more than 40 existing clinical studies of Avandia, suggested that the drug raises the risk of heart attack by 43 percent and cardiovascular death by 64 percent.

"It's a huge risk," Dr. Nissen said in an interview, estimating that "tens of thousands of people" have had heart attacks as a result of taking the medication.

Since 1999, it is estimated that 6 million people in the US have used the drug, with some 1 million Americans currently taking it. Last year, Avandia was one of Glaxo's top-selling drugs, with worldwide sales of more than $3 billion.

Although Glaxo disputed the results of the Cleveland Clinic study, "its own reviews showed the drug increased the risk of heart attack by 30 percent," according to the Associated Press, information the company submitted to the FDA in 2005. It should be noted that any increase in heart attack risk is significant because two thirds of diabetics die of heart-related problems. But the company also presented a study that it said established that Avandia was no riskier than other medication to treat diabetes.

Concerns about the drug date back to 2000, when a letter was written to the FDA by Dr. John B. Buse, chief of endocrinology at the University of North Carolina and currently president-elect of the American Diabetes Association. In the communication, Buse cited "a worrisome trend in cardiovascular deaths and severe adverse events" among patients using the drug. He also accused the company of "blatant selective manipulation of data" in marketing the product.

Dr. Nissen said the cardiovascular risk has been present since the drug's launching. There were, he said, an excess number of cardiovascular events in the registry data given to the FDA during the initial approval process. "Although those events did not reach statistical significance, the data were all going the wrong way." He added: "If I had been a member of the FDA advisory panel that reviewed this drug in 1999, I would have voted against approval and would have asked for more studies to assess cardiovascular risk."

Among the first doctors to raise concerns about the

cardiovascular safety of Merck's Vioxx, Dr. Nissen publicly voiced questions about Avandia in a letter published last December in the British medical journal, the *Lancet*. The researcher's letter took note of increased cardiovascular problems in a 5,000-patient clinical study sponsored by Glaxo. The pharmaceutical company had underwritten the trial in an effort to expand use of the drug to include not only treatment but also prevention of diabetes.

The results were staggering: in the trial, patients taking Avandia had 66 percent more heart attacks, 39 percent more strokes and 20 percent more deaths from cardiovascular-related events compared with placebo. The outcome, wrote Dr. Nissen, "virtually precludes the possibility of an overall benefit and suggests an unexpected mechanism for harm."

Rezulin, another drug in the same class as Avandia, was withdrawn from the market in 2000 because it caused liver problems.

In the May 21 *New England Journal of Medicine* editorial, Drs. Bruce Psaty and Curt Furberg observed: "During the market life of rosiglitazone [Avandia], tens of millions of prescriptions for the drug have been written for patients with type 2 diabetes. Insofar as the findings of Nissen and Wolski represent a valid estimate of the risk of cardiovascular events, rosiglitazone represents a major failure of the drug-use and drug-approval processes in the United States."

The editorial pointed out that on May 10, the Senate passed the Food and Drug Administration Revitalization Act, noting that "none of its provisions [in regard to the drug approval process] would necessarily have identified the cardiovascular risks of rofecoxib [Vioxx] or rosiglitazone [Avandia] in a timely fashion."

Attorneys representing Avandia users say that Glaxo could potentially face tens of billions of dollars in liability. Pharmaceutical analyst Mark Purcell of Deutsche Bank said that "parallels would inevitably to drawn to the ongoing Vioxx litigation," which could assume as much as $10 billion in liability for Merck.