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Research Ties Diabetes Drug to Heart Woes

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by Gardiner Harris

Hundreds of people taking Avandia, a controversial diabetes medicine, needlessly suffer heart attacks and heart failure each month, according to confidential government reports that recommend the drug be removed from the market. The reports, obtained by The New York Times, say that if every diabetic now taking Avandia were instead given a similar pill named Actos, about 500 heart attacks and 300 cases of heart failure would be averted every month because Avandia can hurt the heart. Avandia, intended to treat Type 2 diabetes, is known as rosiglitazone and was linked to 304 deaths during the third quarter of 2009.

“Rosiglitazone should be removed from the market,” one report, by Dr. David Graham and Dr. Kate Gelperin of the Food and Drug Administration, concludes. Both authors recommended that Avandia be withdrawn. The internal F.D.A. reports are part of a fierce debate within the agency over what to do about Avandia, manufactured by GlaxoSmithKline. Some agency officials want the drug withdrawn because they believe there is a safer alternative; others insist that studies of the drug provide contradictory information and that Avandia should continue to be an option for doctors and patients. GlaxoSmithKline said that it had studied Avandia extensively and that “scientific evidence simply does not establish that Avandia increases” the risk of heart attacks.

The battle has been brewing for years but has been brought to a head by disagreement over a new clinical trial and a Senate investigation that concluded that GlaxoSmithKline should have warned patients earlier of the drug’s potential risks. Avandia was once one of the biggest-selling drugs in the world. Driven in part by a multimillion-dollar advertising campaign, sales were $3.2 billion in 2006. But a 2007 study by a Cleveland Clinic cardiologist suggesting that the drug harmed the heart prompted the F.D.A. to issue a warning, and sales plunged. A committee of independent experts found in 2007 that Avandia might increase the risk of heart attack but recommended that it remain on the market, and an F.D.A. oversight board voted 8 to 7 to accept that advice. Hundreds of thousands still take the medicine, although some top endocrinologists say they have sworn off the drug.

Since 2007, more studies have been done. In a December 2009 internal memorandum, Dr. Janet Woodcock, director of the F.D.A.’s drug center, wrote that “there are multiple conflicting opinions” about Avandia within the agency, and she ordered officials to assemble another advisory committee, expected this summer, to reconsider whether the drug should be sold. “I await the recommendations of the advisory committee,” the agency’s commissioner, Dr. Margaret Hamburg, said Friday night. “Meanwhile, I am reviewing the inquiry made by Senators Baucus and Grassley and I am reaching out to ensure that I have a complete understanding and awareness of all of the data and issues involved.”

The bipartisan multiyear Senate investigation — whose results are expected to be released publicly on Monday but which were also obtained by The Times — sharply criticizes GlaxoSmithKline, saying it failed to warn patients years earlier that Avandia was potentially deadly. “Instead, G.S.K. executives attempted to intimidate independent physicians, focused on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that a competing drug might reduce cardiovascular risk,” concludes the report, which was

overseen by Senator Max Baucus, a Montana Democrat, and Senator Charles E. Grassley, an Iowa Republican. Mr. Baucus said of the report, “Patients trust drug companies with their health and their lives, and GlaxoSmithKline abused that trust.”

In response, GlaxoSmithKline said that it disagreed with the Senate investigation’s conclusions. The company said that it could not comment on internal F.D.A. documents but that “the official ruling from F.D.A. is that Avandia remain on the market.” In the wake of the controversy, agency officials ordered GlaxoSmithKline to undertake a study comparing how many heart attacks, strokes and heart-related deaths occur among patients given either Avandia, Actos or a placebo. Studies suggest that Actos, made by Takeda, lowers blood sugar as well as Avandia but without hurting the heart as much.

But Dr. Graham and Dr. Gelperin, working in the F.D.A.’s office of surveillance and epidemiology, argued in two separate internal reports that the new GlaxoSmithKline study, called TIDE, is “unethical and exploitative” because patients given Avandia face far greater risks than those given Actos, with no promise of any additional benefit. The trial may include patients who have had heart attacks or chest pains even though some foreign drug authorities have warned against Avandia’s use by precisely such patients, the reports note. “Although the proposed TIDE trial is motivated by a desire for definitive answers regarding the cardiovascular safety of the drug rosiglitazone, the safety of the study itself cannot be assured and is not acceptable,” one of the reports concludes. These concerns, in internal reports dated October 2008 but not made public until now, were later overruled by other agency officials, and GlaxoSmithKline is currently enrolling patients in the TIDE trial. The trial is not expected to be completed until 2020, although the company is hoping to report some results to the F.D.A. by 2014. The company’s patent on Avandia expires in 2012, and generic versions will probably swallow most remaining profits.

In a letter sent Thursday to Dr. Hamburg, the Food and Drug Administration commissioner, Mr. Baucus and Mr. Grassley asked “what steps the F.D.A. has taken to protect patients in the TIDE trial” and said the trial’s patients had never been told about the concerns raised by the agency’s own safety officers. Mr. Grassley said the internal agency battle showed that the agency needed to be restructured to give more power to safety officials like Dr. Graham and Dr. Gelperin over their counterparts who approve medicines and deal more directly with drug makers. “It doesn’t make any sense to have these experts who study drugs after they have been on the market for several years under the thumb of the officials who approved the drug in the first place and have a natural interest in defending that decision,” Mr. Grassley said. “The Avandia case may be the most alarming example of the problem with this setup.”

The question of when and how to communicate possible drug risks has long bedeviled drug makers and regulators. Hints are common that drugs may cause injuries; thousands of drug injury reports pour into the Food and Drug Administration every week. For example, Avandia ranked first among all prescribed drugs in the number of serious, disabling and fatal problems — including 304 deaths — reported to the agency in the third quarter of 2009, according to an analysis done by the Institute for Safe Medication Practice, a drug safety oversight group.

But companies say that such reports do not offer proof of a problem and that highlighting them can scare patients away from needed treatment, so they often argue that more certainty is needed before alarms are raised. GlaxoSmithKline said a “vast majority” of the recent reports regarding Avandia was related to litigation. The Senate investigation — the result of years of digging through more than 250,000 internal company documents — concludes that GlaxoSmithKline and by extension the F.D.A. delayed far too long in this process.

In November 2003, for instance, the company completed a study in which diabetics given Avandia had far more heart problems than those given placebos. Two months later, the World Health Organization sent the company an alert linking Avandia to heart ailments. In a June 2004 meeting, the company's Global Safety Board said a hard look should be taken at all Avandia clinical trials for more signs of heart problems, documents show.

European regulators had earlier ordered GlaxoSmithKline to conduct a study — called the Record trial — to examine Avandia's heart risks because hints of these problems appeared in the company's earliest trials.. But the Senate report shows that by at least 2004, company executives were aware that the Record trial was going so poorly that it would never answer the heart question with any kind of certainty.

So company executives gathered dozens of Avandia studies and sifted their combined data. Called a meta-analysis, this combined look found first in 2005 and in an updated look in 2006 that Avandia increased the risks of serious heart problems by nearly a third, the Senate investigation shows. Because two-thirds of diabetics die of heart problems, this was hugely worrying. In 2005, executives revealed the results of their meta-analysis to the F.D.A., and in 2006 they provided the agency with the underlying data.

Two large company-sponsored trials — called Dream and Adopt — were published near the end of 2006, and each provided more hints that Avandia hurts the heart, the documents show. In a March 2007 meeting of the company's Diabetes Franchise Cardiology Advisory Board, advisers called the safety worries found in these many studies "disquieting." Negotiations with agency officials about how and whether to alert the public continued. Meanwhile, the company continued to market and advertise Avandia aggressively. The Senate inquiry concludes that the company threatened doctors who suggested in public that Avandia might have serious risks.

In 1999, for instance, Dr. John Buse, a professor of medicine at the University of North Carolina, gave presentations at scientific meetings suggesting that Avandia had heart risks. GlaxoSmithKline executives complained to his supervisor and hinted of legal action against him, according to the Senate inquiry. Dr. Buse eventually signed a document provided by GlaxoSmithKline agreeing not to discuss his worries about Avandia publicly. The report cites a separate episode of intimidation of investigators at the University of Pennsylvania.

GlaxoSmithKline said that it "does not condone any effort to silence" scientific debate, and that it disagrees with allegations that it tried to silence Dr. Buse. Still, it said the situation "could have been handled differently."