US panel wants changes to Avandia safety measures (Update)

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US government health experts are recommending changes to safety restrictions on former blockbuster diabetes pill Avandia, in light of a new analysis suggesting that the drug may not increase the risk of heart attack as previously believed.

A majority of Food and Drug Administration advisers voted Thursday to modify or remove measures that currently limit patient access to GlaxoSmithKline's Avandia. Among other requirements, patients currently must sign a waiver that they understand the drug's risks before getting a prescription.

The panel ruling is a belated victory for British drugmaker Glaxo after more than a half-decade defending the safety of its product, which was once the best-selling diabetes drug in the world. Sales began plummeting in 2007 after researchers first raised questions about possible links to heart attack. After three years of debate, the FDA limited access to the drug in 2010 and European regulators banned the pill altogether.

Of the panel's 26 experts, 13 voted to modify safety restrictions on Avandia while seven voted to remove them entirely. Five panelists voted to keep the measures in place without any changes, while one panelist voted to withdraw Avandia completely.

The vote is a recommendation to the FDA and is not binding.

The FDA convened this week's two-day meeting to consider a new

analysis of Avandia's cardiovascular safety performed by Duke University's Clinical Research Institute.

Researchers there reexamined the lone GlaxoSmithKline PLC study specifically designed to measure Avandia's heart risks. The original study's results have been called into question since they were first released in 2009, due to design flaws and inconsistent reporting of heart attacks. Panelists said the reanalysis bolstered their confidence that Avandia does not increase the risk of heart attack more than older diabetes medicines.

"I'm considerably reassured, in light of the reanalysis, that the magnitude of risk we're talking about here is not very great," said Dr. Dale Hammerschmidt of the University of Minnesota, who voted to modify the safety limits.

Under the FDA's current risk-evaluation management strategy, or REMS, Avandia can only be dispensed by specially pharmacies. Like patients, physicians must sign a waiver stating that they understand the drug's risks and that their patients have not responded to any other diabetes medications. Those requirements have essentially cratered prescriptions for the drug. Just 3,000 people in the U.S. are currently taking Avandia, down from 250,000 in 2010. Many panelists said they now believe the restrictions are too severe.

"I believe relaxing the REMS would put this on a more even playing field with other drugs with similar risks," said Dr. Elaine Morrato, of the University of Colorado.

Most panelists said some restrictions are still warranted, such as patient brochures discussing the drug's risks. Panelists also favored registering patients to track their health while on Avandia.

Glaxo's chief medical officer said in a statement: "We continue to believe that Avandia is a safe and effective treatment option for type 2 diabetes."

But even if regulators relax limits on Avandia, it's highly unlikely the drug will regain its blockbuster status.

"It's very difficult to rehabilitate a drug, any drug, after it's been through a process like this," said Rebecca Killion, the panel's patient representative.

This week's meeting marked the third time that the FDA assembled its experts to answer a seemingly basic question: Does Avandia increase the risk of heart attacks? A firm answer has proved elusive, in part because patients with diabetes are already predisposed to heart problems. That makes it extremely difficult to tell which heart attacks are drug-related and which are simply a result of the underlying disease.

The initial concerns about Avandia came from outside researchers who pooled thousands of reports of heart attack and stroke from dozens of unrelated studies. One of these so-called meta-analyses combined 42 studies and appeared to show a higher risk of heart attack among patients taking Avandia compared to other diabetes drugs.

The FDA added a boxed warning about heart attack risks to Avandia in 2007, while noting the shortcomings of the analysis that produced the concern. FDA leadership generally argues that mixing data from multiple studies can lead to misleading trends and conclusions. The agency tries to base its decisions on head-to-head controlled clinical trials, which most medical experts consider the gold standard of research.

That has focused the agency's attention on the RECORD trial, a six-year

study of 4,400 patients that compared heart attack rates in patients taking Avandia versus metformin and sulphonylurea, a standard drug combination for diabetics. The initial results reported by Glaxo in 2009 showed no signal for heart attacks, but those findings have been questioned because of missing data and other issues.

Under instructions from the FDA, Glaxo hired Duke University to reanalyze the RECORD study, reviewing each report of heart attack or stroke at a patient-by-patient level. Duke's findings matched Glaxo's initial conclusion: Avandia did not appear to increase the risk of heart attack.

At least one FDA reviewer said this week that Duke's review was not truly independent, since the university was paid $3 million by Glaxo and relied on records provided by the drugmaker.

FDA leadership said there was no evidence of "systematic or intentional manipulation" of the RECORD reevaluation. The agency's panelists almost uniformly backed that conclusion.