FDA hearings leave doctors, patients in limbo on Avandia

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Amidst allegations of concealed data, increased health risks and biased trials, two days of hearings into the safety of a leading type 2 diabetes drug have left doctors and patients in limbo about continuing to prescribe or take the medicine.

A majority of the 33 experts meeting in Washington, DC July 13 and 14 advised the United States Food and Drug Administration either to withdraw rosiglitazone (Avandia) or add sterner warnings and restrict its use. During a complicated series of nine votes, 12 of the 32 committee members who voted (one abstained) recommended taking the controversial drug off the market. Ten others advised allowing its continued sale, but voted for the warnings.

In another vote, 18 of 31 experts found evidence that rosiglitazone raises the risk of heart attack relative to older medicines and to piaglitazone (Actos), its major competitor.

Two Canadian researchers at the heart of the US debate, and on different sides of it, agreed afterward that the primary result of the hearings was enduring confusion and, as one of them put it, "a Gordian knot" for regulators.

The FDA now has to decide what to do about the widely prescribed drug, which already contains "black box" warnings to physicians about the risks.

The recommendations, which are not binding, also leave Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, in a quandary about whether to continue a major trial, known as the Thiazolidinedione Intervention in Vitamin D Evaluation (TIDE) trial, comparing rosiglitazone with piaglitazone. Most of the committee voted that if the drug was to stay on the market, the trial should continue.

"FDA takes the committee's advice very seriously,'' Woodcock said following the hearings. "We will come to a decision as soon as possible and announce that publicly." The FDA usually follows the prevailing views of its expert panels.

Kevin Lamarque/Reuters

A majority of the 33 experts who met in Washington, DC, on July 13–14 advised the US Food and Drug Administration to either withdraw rosiglitazone (Avandia) from the market or add sterner warnings and restrict use.

The FDA held the public hearings to clarify rosiglitazone's safety profile, following calls to remove it from the market by some prominent US and Canadian researchers, including David Juurlink, a researcher with the Institute of Clinical Evaluative Science. Health Canada has said it is closely watching the FDA's decision.

Juurlink and others argue rosiglitazone has no demonstrable advantage over piaglitazone, which also works to lower blood sugar and seems to cause or contribute to fewer heart problems.

"I'm mystified as to what happens now," Juurlink told *CMAJ*. "You have a Gordian knot of sorts for the FDA. You have 12 people saying the drug should come off the market, and 10 people saying it should stay on the market but largely be restricted to people who cannot tolerate Actos. Even if you are skeptical of the harm data … how can you justify giving the patient Avandia when it has no advantage over Actos?"

Juurlink believes the committee's advice is "irreconcilable." He questions the ability of TIDE's investigators to continue the randomized trial given that patients in one group would be receiving a drug the FDA experts want more tightly restricted.

"The message is that the committee has left Avandia on life support," Juurlink says. "Exactly when to pull the plug is now in the hands of the FDA."

The principal investigator of the TIDE trial, Dr. Hertzel Gerstein of McMaster University in Hamilton, Ontario, agreed that the hearings have only muddied the issue. But he believes the trial needs to continue to resolve the uncertainties.

"The major message that comes across from this is one of confusion," Gerstein says. "Science is not deter-

mined by voting. The fact that you have two-thirds of the people voting to leave the drug on the market and one-third of the people voting to withdraw the drug from the market is, to me, evidence of uncertainty."

The way to resolve that uncertainty is to continue the TIDE trial — and the steering committee of 45 experts running the study for the manufacturer, GlaxoSmithKline, has decided to go forward, he says.

Testimony at the hearings revealed a split within the FDA between drug reviewers charged with determining rosiglitazone's post-market safety, and reviewers working in the office that initially allowed the drug on the market in 1999. That arm of the FDA receives money from the pharmaceutical industry to conduct its reviews.

FDA reviewer David Graham, who has long been critical of rosiglitazone, argues that it has no benefits over piaglitazone and should be withdrawn on that basis alone. Its risks, on the other hand, are real enough "to put you in a hospital or a cemetery," he told the hearings.

Other reviewers accused GSK of hiding problems with rosiglitazone found in an earlier study and dropping patients who experienced cardiac events from yet another trial, called RECORD.

But Dr. David Capuzzi, another panel member, argued the case against rosiglitazone is not "drag-down complete" and "it would be a disaster" to pull a useful drug from the market in this circumstance. Panelist Rebecca Killion, an FDA patient representative, agreed, saying: "This drug is not for everybody, but that may not mean it's not for anybody."

On the eve of the hearings, GlaxoSmithKline settled millions of dollars worth of Avandia lawsuits launched by patients and family members in the United States. A Canadian class-action lawsuit continues to wind its way through the courts.

After the hearings the Endocrine Society, the American Diabetes Association and the American Association of Clinical Endocrinologists issued a statement urging patients already taking rosiglitazone not to change their medication without discussing it with their doctor. — Laura Eggertson, Ottawa, Ont. and Cal Woodward, Washington, DC

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