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Quick Pulse

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FDA Orders New Black Box Warning for Diabetes Drug Avandia – but Leaves It on the Market

The FDA announced on November 14, 2007, that the black box warning on GlaxoSmithKline's Avandia (rosiglitazone), a thiazolidinedione (TZD) for Type 2 diabetes, is being strengthened to include new information about an increased risk for heart attacks, but the Agency did not find the risk sufficient to withdraw Avandia from the market. The FDA also asked GSK to:

1. Conduct a four- to five-year study comparing Avandia to other oral anti-diabetes drugs and urged Type 2 diabetics with underlying heart disease or who are at high risk of heart attack and who are taking Avandia to discuss the drug with their doctor.
2. Add the same warning to its Avandamet (rosiglitazone + metformin) and Avandaryl (rosiglitazone + glimepiride).
3. Develop a Medication Guide for patients to provide additional information about the benefits, risks, and safe use of Avandia.

The black box label includes this new language:

> "A meta-analysis of 42 clinical studies (mean duration six months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with increased risk of myocardial ischemic events such as angina or myocardial infarction (MI). Three other studies (mean duration 41 months; 14,067 patients) comparing Avandia to other approved oral anti-diabetes drugs, or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive."

According to Dr. Janet Woodcock, the FDA's deputy commissioner for scientific and medical programs, chief medical officer, and acting director of the Center for Drug Evaluation and Research (CDER), the language conforms to the recommendations of the Endocrinologic and Metabolic Drugs Advisory Committee which met jointly with the Drug Safety and Risk Management Advisory Committee on July 30, 2007. That panel voted 20 to 3 that Avandia increases cardiac ischemic risk in Type 2 diabetics, and they voted 22 to 1 that instead of pulling the drug, the FDA should require strong, new warnings or black boxes in the label. Dr. Woodcock said, "This basically lines up with what the advisory committee told us."

After the panel meeting, the FDA held internal meetings about what action to take. Dr. Woodcock said, "It was clear that in the advisory committee there were different opinions regarding appropriate regulatory action. Therefore, the issue

was referred to the drug safety oversight board (an internal federal board made up of FDA representatives as well as other federal employees) for advice. This board was split in its vote, but overall they felt that the drug should stay on the market, and their recommendation was given to the center director."

The FDA's decision was based on a meta-analysis of short-term studies showing a relationship between Avandia and an increase in MI, despite inconclusive evidence or a lack of evidence in three long-term studies. Dr. Woodcock called the announcement "an update to the existing box warning to Avandia," adding, "The black box is the strongest form of warning, and we are adding another statement to that warning …This whole issue of cardiac ischemia is complicated. Some six months or so ago, studies in the (meta-analysis) showed risk of increased cardiac ischemia, but three larger clinical studies comparing Avandia to other diabetes treatments did not show a similar finding…The FDA is trying to sort out the reasons for these differences in the results, including whether they were due to study design, different comparisons, different patient populations…or the duration of the studies."

Dr. John Jenkins, director of the FDA's Office of New Drugs in CDER, made several points:

- "The meta-analysis of the 42 clinical studies did seem to show an increased risk of myocardial ischemia, including things like myocardial infarctions, and as we looked at the data, it seems that much of the difference was seen compared to placebo."
- "When we looked at the three long-term studies – Avandia compared to other active therapies – a similar finding was not observed. In fact, in some of those studies the overall mortality – overall number of deaths – tended to favor those patients randomized to receive Avandia."
- "The overall message that we have is that we have a signal from the short-term trials in the meta-analysis, largely driven by comparison to placebo. When we look across the larger studies, compared to other oral anti-diabetic agents, we don't see the same findings, and that's why we reached the conclusion we have."
- "It's important to understand that patients with diabetes need therapy, so placebo is not an option for long-term care of patients with diabetes. As we look at the data, we need to understand the risks of the drugs and their benefits."
- "Clearly there has been a signal of concern raised for Avandia from the meta-analysis, but as we look at the entire data, they are inconclusive. We want to make sure that healthcare providers and patients are aware that this signal of risk has been identified and, while waiting for more definitive studies to be completed, make sure they take them into account as they make their decisions."

The Avandia label also is being updated to advise that Avandia is not recommended, though not contraindicated, for use by patients taking insulin or nitrates.

New Avandia study required

FDA officials said they are keeping Avandia on the market because there is not enough evidence showing the risk of heart attack or cardiac ischemia is higher for Avandia than for other Type 2 diabetes treatments, but the Agency wants more data. Dr. Woodcock said, "We directed GSK to conduct a long-term study…We're working with GSK to make sure the study is started and completed in a timely manner."

The FDA is still negotiating with GSK about the trial details, but it will be a randomized study. Dr. Jenkins said, "We have reached agreement that they will conduct a study and the timeline for the study. Some of the fine point details about the comparison groups and other aspects still need to be discussed and agreed to, and those haven't been finalized yet…We expect pioglitazone (Takeda's Actos) to be one of the comparators, but even if the trial were started head-to-head comparing it (Actos) to Avandia, many of those patients would still need other drugs added to help control their diabetes, so this will likely be a long-term study and could take as long as four or five years, so over time there will be multiple comparisons."

Dr. Mary Parks, deputy director of the FDA's Division of Metabolic and Endocrine Drug Products, said the FDA wants to be sure the study provides the information the Agency needs, "None of the approved therapies have demonstrated they can reduce cardiovascular (CV) risk, and these trials would take a very long time to conduct because of the complexity of disease. It is very important to make sure the appropriate, adequate study and comparators are selected… When the study is concluded, we want to make sure it was the right study, right design, and right comparators to make sure we get the right answers."

Dr. Jenkins said that the FDA expects the study's final protocol to be submitted no later than the end of July 2008. The FDA expects the study to start by the end of November 2008 and to be completed (final study report) by the end of March 2014.

Other anti-diabetic drugs will not get same warning or trial requirement

Avandia is the only diabetic medication getting this strengthened black box warning. Asked if the other drug in the TZD class – Actos – should also have the additional language, Dr. Woodcock said, "(Avandia) hasn't been compared head-to-head with the only other single drug in the class. However, most diabetics are started on metformin or other drugs, and the data comparing those against this drug do not show differences."

In other words, the FDA is ***not*** going to ask Takeda, the manufacturer of Actos, for a similar study, and Actos is not getting a similar black box warning about heart attacks. Dr. Woodcock said, "(Takeda) has completed a study in a patient population – a fairly long-term study – and did not reveal an increased risk."

A 16,309-patient meta-analysis of 19 clinical trials, published in September 2007 in the ***Journal of the American Medical Association*** by Dr. A. Michael Lincoff and colleagues at the Cleveland Clinic, concluded that Actos not only did not increase the risk of CV events but was associated with a significantly lower risk of heart attack, stroke, or death (the primary endpoint) vs. control. Death, MI, or stroke occurred in 4.4% of Actos patients and 5.7% of control patients (p=0.005). The time-to-event curves separated at about 1 year, and individual components of the primary endpoint were all reduced similarly. However, the analysis did find an expected increase in congestive heart failure with Actos (2.3% vs. 1.8% for control, p=0.002) as with Avandia.

Asked about the risk of heart disease in patients taking Avandia compared to patients on other anti-diabetic drugs such as sulfonylureas, Dr. Woodcock said, "The sulfonylureas have had black box warnings since the 1970s about the risk of cardiovascular death. So, those have long been under some question about whether – based on trial data – they raise the risk…The question about whether one (drug) has increased risk of cardiovascular problems over another, first of all, would be very hard to detect, but don't forget that all drugs have a variety of benefits and risks associated with them, so a benefit:risk analysis would have to be undertaken any time we get new findings."

However, all oral anti-diabetic drugs are getting one label change. All the labels must now contain language describing the lack of data showing any cardiovascular benefit. Dr. Jenkins explained, "We plan to ask all the manufacturers of the oral anti-diabetic medications to add the statement: **'To date no oral anti-diabetic drugs have been conclusively shown to reduce cardiovascular risk.'** The pioglitazone labeling includes information about the PROactive study, done as an outcome study, and our interpretation and review of that study is that it didn't show conclusive evidence of reduced cardiovascular risk…That study did not meet its primary objective…There were some trends discussed at the advisory committee, but the prime endpoint didn't show a decrease in cardiovascular risk, so it will have the (disclaimer)…We want to add into the label of other agents the statement making clear that none has been clearly shown to reduce cardiovascular risk."

Asked if pioglitazone might have greater risk compared to other anti-diabetic drugs, Dr. Jenkins said, "The number of studies – head-to-head comparisons of rosiglitazone to pioglitazone – is only a few, and they have been very small, so there is not an adequate basis to make any findings or comparisons between those two drugs."

GSK's response

After the announcement, Dr. Ronald Krall, GSK's chief medical officer, said, "Avandia remains a safe and effective medicine for most patients with Type 2 diabetes when used appropriately…We will continue to work with the FDA to conduct more studies about the safety and benefits of our medicine."

GSK also emphasized that two long-term trials in diabetic patients – ADOPT and RECORD – as well as a long-term trial in pre-diabetics (DREAM) showed no increased risk for CV events compared to other commonly used medications, other than the well-known risk of congestive heart failure with TZDs. GSK insisted that it believes data from ongoing and future clinical trials will provide additional scientific support for both the benefit and safety of Avandia, which has been prescribed to more than seven million people since it was approved in 1999.

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