U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication

FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines

This update is in follow-up to the FDA Drug Safety Communications issued on November 4, 2011, and May 18, 2011.

Safety Announcement

[11-25-2013] The U.S. Food and Drug Administration (FDA) has determined that recent data for rosiglitazone-containing drugs, such as Avandia, Avandamet, Avandaryl, and generics, do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. As a result, we are requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on our review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI).

Type 2 diabetes is a disease that can lead to serious complications and premature death. Rosiglitazone is a treatment option that can improve blood sugar control in some patients with the disease. Patients with type 2 diabetes should continue to work closely with their health care professionals to determine treatment options that are most appropriate.

FDA continues to evaluate the safety and effectiveness of drugs after they go on the market. In the case of rosiglitazone medicines, previous data from a large, combined analysis of mostly short-term, randomized clinical trials of rosiglitazone had suggested an elevated risk of heart attack, so we required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The Rosiglitazone REMS program restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks.

Although some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains, in light of the new re-evaluation of the **R**osiglitazone **E**valuated for **C**ardiovascular **O**utcomes and **R**egulation of Glycemia in **D**iabetes (RECORD) trial, our concern is substantially reduced and the rosiglitazone REMS program requirements will be modified (see Data Summary). We are also requiring revisions to the rosiglitazone

prescribing information and the patient Medication Guide to include this new information.

Under FDA's proposed modifications to the rosiglitazone REMS program:

- Distribution of the medicines will no longer be restricted. Rosiglitazone may be used along with diet and exercise to improve control of blood sugar in patients with type 2 diabetes mellitus.
- Health care professionals, pharmacies, and patients will no longer be required to enroll in the rosiglitazone REMS program to be able to prescribe, dispense, or receive rosiglitazone medicines.
- As part of the REMS, health care professionals who prescribe rosiglitazone medicines will be required to have training about the current state of knowledge concerning the cardiovascular risk of rosiglitazone medicines. Manufacturers will also send Dear Healthcare Provider and Dear Professional Society letters to educate prescribers about the new information.

Data Summary

Previous meta-analyses (large, combined analyses) of trials and observational studies suggested an increased risk of heart attack and other adverse cardiovascular events with rosiglitazone treatment. As a result, FDA required a REMS that restricted the drug's use. Due to limitations of those data, in 2010 FDA required a comprehensive readjudication (expert re-evaluation) of the results from the RECORD trial. DCRI conducted this readjudication. RECORD was a clinical trial requested by the European Medicines Agency and conducted after rosiglitazone was approved for marketing. RECORD compared the cardiovascular safety of rosiglitazone used in combination with metformin or sulfonylurea to the combination of metformin and sulfonylurea. Metformin and sulfonylurea are other medicines approved to treat diabetes. The original evaluation of RECORD suggested an increase in heart attacks and decreases in the rates of death and stroke in patients treated with rosiglitazone.

These results were not statistically significant, which means it is uncertain whether the changes in risk for patients treated with rosiglitazone were due to the drug or due to chance alone. During the course of FDA's original 2010 review of the RECORD trial, important questions had arisen about potential bias in the identification of cardiovascular events. FDA required this independent review to provide clarity about the integrity of the findings. FDA reviewed DCRI's readjudicated results, and the findings were later discussed at a June 5-6, 2013, joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (for complete background information and safety reviews, see AC Meeting.

The readjudicated results could not dismiss an increased risk of heart attack with rosiglitazone versus placebo, because the trial did not use a placebo. However, the readjudicated results did assess rosiglitazone versus the standard-of-care diabetes drugs metformin and sulfonylurea and confirmed the original RECORD finding that did not show an increased risk of heart attack associated with rosiglitazone. In the trial, patients treated with rosiglitazone experienced fewer deaths from a cardiovascular cause, from a stroke, and from a heart attack; fewer nonfatal strokes; and fewer deaths from any cause compared to patients treated with metformin and sulfonylurea. Patients treated with metformin and sulfonylurea had fewer nonfatal heart attacks compared to patients treated with rosiglitazone. However, none of these results were statistically significant, which means it is not clear whether the risk of death, heart attack, and stroke were truly different between rosiglitazone and metformin plus sulfonylurea. Based on the results of the readjudicated RECORD trial, FDA is requiring modifications to the rosiglitazone REMS program to remove the requirements for restricted distribution.