

FDA Drug Safety Communication: Ongoing review of Avandia (rosiglitazone) and cardiovascular safety

Safety Announcement

[02-22-2010] The U.S. Food and Drug Administration (FDA) is reviewing data, submitted in August 2009, from a large, long-term clinical study on possible risks with the diabetes drug, Avandia* (rosiglitazone). The clinical study, called the **R**osiglitazone **E**valuated for **C**ardiovascular **O**utcomes and **R**egulation of Glycemia in **D**iabetes or RECORD study was designed to evaluate the cardiovascular safety of rosiglitazone, a medication used to treat type 2 diabetes mellitus.

In addition to the RECORD study, a number of observational studies of the cardiovascular safety of rosiglitazone have been published. FDA has been reviewing these on an ongoing basis.

FDA is now reviewing the primary data from the completed RECORD study, conducting follow-up audits, and reviewing additional studies. This work is ongoing and no new conclusions or recommendations about the use of rosiglitazone in the treatment of type 2 diabetes have been made at this time.

Once FDA completes its review of the data from the RECORD study, the agency will present the totality of new and existing cardiovascular safety data on rosiglitazone at a joint public meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees in July 2010. At that meeting, the Advisory Committee will provide an updated assessment of the risks and benefits of rosiglitazone in the treatment of type 2 diabetes.

When prescribing rosiglitazone, healthcare professionals should follow the recommendations in the drug label. Patients should continue taking rosiglitazone unless told by their healthcare professional to stop. Patients who are concerned about the possible risks associated with using rosiglitazone should talk to their healthcare professional.

FDA previously communicated to the public about the possible association between rosiglitazone and increased cardiovascular risk in a [2007 safety alert](#)¹. The agency also sought advice from external experts at the [July 30th 2007](#)² joint meeting of the FDA Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. The RECORD study data represent the only new information from a completed randomized, controlled clinical trial of rosiglitazone received by FDA since the 2007 announcements.

The RECORD study was designed to evaluate the cardiovascular safety of rosiglitazone, which is consistent with FDA's December 2008 [Guidance for Industry](#)³ recommending that manufacturers of new treatments for diabetes carefully design their clinical trials to include an evaluation of cardiovascular safety. The RECORD study will be evaluated in the context of this recent Guidance.

** Rosiglitazone is sold as a single-ingredient product under the brand name Avandia. It is also available in combination with other diabetes medications, metformin under the brand name Avandamet or glimepiride under the brand name Avandaryl.*

Additional Information for Patients

FDA recommends that patients currently using rosiglitazone:

- Not stop taking their medication without talking with their healthcare professional.
- Discuss any questions or concerns they have about rosiglitazone with their healthcare professional.
- Read the *Medication Guide* that comes with each rosiglitazone prescription to better understand the risks and benefits of their medication.
- Report any side effects with rosiglitazone to FDA's MedWatch program using the information at the bottom of the page.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals:

- Follow the recommendations in the drug label when prescribing rosiglitazone. This includes a *Boxed Warning* stating that:
 - Use of rosiglitazone in patients with established NYHA Class III or IV heart failure is contraindicated. Further, rosiglitazone is not recommended in patients with symptomatic heart failure.
 - Rosiglitazone causes or exacerbates congestive heart failure in some patients. Healthcare professionals should monitor for the signs and symptoms of heart failure (including excessive, rapid weight gain, difficulty breathing, and/or swelling) after starting treatment and after dose increases of rosiglitazone. If heart failure signs and symptoms occur, the heart failure should be managed appropriately and discontinuation or dose reduction of rosiglitazone must be considered.
 - Available data on rosiglitazone and risk of myocardial ischemia are inconclusive. A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, found an association between rosiglitazone use and an increased risk of myocardial ischemic events such as angina or heart attack. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to other oral diabetes medications or placebo, have not confirmed or excluded this risk. The recently completed RECORD study, currently being reviewed by FDA, is one of these three studies.
- Discuss with patients the risks of rosiglitazone treatment, taking into account the clinical utility of rosiglitazone, the risks/benefits of other antidiabetic medications, and the risks associated with poorly controlled blood glucose.
- Discuss with patients the importance of adhering to their diabetes medication regimen.
- Report any adverse events associated with the use of rosiglitazone to FDA's MedWatch program using the information at the bottom of the page.

Data Summary

Part of a post-approval commitment between the European Medicines Agency (EMA) and the manufacturer, the RECORD study compared cardiovascular safety outcomes in 2,220 patients with type 2 diabetes taking rosiglitazone plus other diabetes medications (metformin or a sulfonylurea) to 2,227 patients taking metformin and a sulfonylurea.

Patients in the study were followed on average 5.5 years and were monitored for the occurrence of the primary endpoint (cardiovascular death and cardiovascular hospitalizations). There were several secondary endpoints including the composite endpoint for major cardiovascular events (cardiovascular death, heart attack or stroke). All CV endpoints were determined by a team of cardiologists who were unaware of which patients were receiving rosiglitazone. The study reported no difference in the primary endpoint in the rosiglitazone group [hazard ratio = 0.99 (95% Confidence Interval of 0.85 to 1.16)] compared to combined use of metformin and a sulfonylurea. In addition, there was no significant treatment difference in any of the secondary composite endpoints except an increase in heart failure, which is a well-known side effect of drugs in this class, including Actos (pioglitazone). The increase in risk of heart failure is consistent with the warnings contained in the current drug label. The RECORD study findings were published in the June 2009 issue of *Lancet*¹.

FDA will present a summary of any new observational studies of rosiglitazone safety at the upcoming Advisory Committee meeting in July 2010.