



## Rosiglitazone maleate (marketed as Avandia)

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**FDA ALERT [5/2007]:** FDA is aware of a potential safety issue related to Avandia (rosiglitazone maleate). Safety data from a pooled analysis of controlled clinical trials have shown a significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia. However, other published and unpublished data from long-term clinical trials of Avandia provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking Avandia. FDA's review of all available data is ongoing. FDA has not confirmed the clinical significance of the reported increased risk of ischemic cardiovascular events in the context of other studies. Myocardial ischemic events are currently described in the WARNINGS section of the [Avandia label](#). FDA does not know whether the other approved medication in the same pharmacologic class or other oral drugs for treating type 2 diabetes have less, the same, or greater risks. Switching diabetic patients to other therapies also confers its own risks. For those reasons, FDA is providing this emerging information to prescribers so that they and their patients can make individualized treatment decisions.

*This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging drug safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing the product. FDA is considering, but has not reached a conclusion about, whether this information warrants any regulatory action. FDA intends to update this sheet when additional information or analyses become available.*

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*To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this page.*

FDA has received additional safety information, a pooled analysis of 42 clinical studies for the treatment of type 2 diabetes mellitus, from the manufacturer of Avandia, GlaxoSmithKline. The data from these studies and the associated analyses are complex and are currently being reviewed by the FDA. In the meantime, FDA is providing information on the initial results of these analyses. The degree of risk of Avandia related to ischemic cardiovascular events is not yet certain.

### Recommendations and Considerations

Avandia's current prescribing information includes data in the WARNINGS section about cardiac adverse events (congestive heart failure and ischemic events). These warnings can be found in the current prescribing information available at: <http://www.fda.gov/cder/foi/label/2007/021071s0231bl.pdf>. Healthcare professionals should consider this and other available data when making individual treatment decisions for their patients with type 2 diabetes.

### Background Information and Data



Report serious adverse events to FDA's MedWatch reporting system by completing a form on line at <http://www.fda.gov/medwatch/report/hcp.htm>, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided on line (5600 Fishers Lane, Rockville, MD 20853-9787), or by telephone (1-800-FDA-1088).



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FDA has received data from several different clinical studies of Avandia for treatment of type 2 diabetes. These studies vary with respect to the study design (e.g., pooled analysis, individual randomized controlled clinical trial, observational epidemiological study), patient populations enrolled, treatment groups, and length of patient follow-up. The studies analyzed to date have shown different rates of ischemic cardiovascular events. Based on these data, the risk of ischemic cardiovascular events remains unclear. Following are summaries of the studies and data.

### **Clinical Trial Data - Pooled Analysis of 42 Studies**

FDA has received the pooled data from 42 separate double-blinded, randomized controlled clinical trials to assess the efficacy of Avandia for treatment of type 2 diabetes compared to a variety of alternative therapies. The combined studies included 8,604 patients on Avandia and 5,633 patients randomized to a variety of alternative therapeutic regimens, including placebo. In general, these studies had differing primary efficacy endpoints; they were not designed to thoroughly investigate cardiovascular safety. Treatment groups varied and included Avandia alone or in combination with insulin, sulfonylureas, and/or metformin. The comparator arms were varied and included placebo alone or as an add-on treatment to other anti-diabetic agents, and other active anti-diabetic treatment regimens. The combined patient population was diverse, including patients with average duration of diabetes ranging from 5 to 13 years as well as patients with significant risk factors for cardiovascular disease (e.g., history of myocardial infarction, bypass surgery, stroke, peripheral vascular disease, and NYHA Class 1 and 2 heart failure). All but four studies were of six months in duration. In this pooled analysis as submitted by GlaxoSmithKline, the overall incidence of myocardial ischemia in Avandia-treated subjects relative to the comparators was 1.99% vs. 1.51% with a hazard ratio of 1.31 (95% CI 1.01-1.70). This risk equates to a more than 30% excess risk of myocardial ischemic events in Avandia-treated patients.

### **Balanced Cohort Study of Coronary Heart Disease Outcomes in Patients Receiving Anti-diabetic Agents**

The Balanced Cohort Study is an observational study of 33,363 patients using a managed care database. Propensity matching was used to match risk factors for cardiovascular disease and other considerations for patients initiating therapy. About 90% of the patients had no history of cardiovascular disease. The composite cardiovascular endpoint was hospitalizations for myocardial infarction and coronary revascularization. Patients included in this study began treatment with Avandia between 2000 and 2004. The treatment groups were monotherapy with Avandia, metformin, or sulfonylurea; oral dual therapy combinations, and insulin combinations. Follow-up was 1.2 years. The incidence of the composite cardiovascular endpoint was 1.75



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events per 100 patient-years for the Avandia-containing regimens and 1.76 events per 100 patient-years for other treatments (hazard ratio 0.93; 95% CI 0.80-1.10).

### **A Diabetes Outcomes Progression Trial (ADOPT)**

ADOPT is a randomized, double-blind study of 4,351 patients that compared rosiglitazone, metformin, or glyburide monotherapy on the improvement of and maintenance of glycemic control in patients newly diagnosed with type 2 diabetes. Patients with underlying cardiovascular disease were excluded. Median follow-up was 4 years. The myocardial ischemic event hazard ratios for rosiglitazone vs. metformin; rosiglitazone vs. glyburide; and metformin vs. glyburide were 0.96 (95% CI 0.66, 1.38), 1.16 (95% CI 0.78, 1.73) and 1.22 (95% CI 0.082, 1.80), respectively. The results of the ADOPT trial have been published, see the *New England Journal of Medicine* 355;23 pg 2427-2443 December 7, 2006. These data do not support an ischemic risk of rosiglitazone relative to metformin (the first line therapy for type 2 diabetes and a drug that has been shown to lower long term cardiovascular risk).

### **The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Study**

The DREAM study is a placebo-controlled, randomized, double-blind clinical trial in pre-diabetic patients designed to determine if the use of early treatment with medication could forestall the development of overt type 2 diabetes. The study was conducted in nearly 5,300 patients who were randomized to either rosiglitazone or placebo and were followed-up for a mean duration of 3 years. The study also was intended to examine whether Avandia and/or ramipril delayed onset of overt type 2 diabetes. Therefore the trial used a factorial design, with patients randomized to any of four treatment arms: placebo with placebo; rosiglitazone with placebo; placebo with ramipril; and rosiglitazone with ramipril. This study, as reported in the *Lancet*, showed an effect of rosiglitazone in delaying the development of type 2 diabetes (not found with ramipril) in these prediabetic patients. GSK has shared with FDA an analysis of the data for Avandia alone versus placebo which showed no increased risk of myocardial infarction, stroke or cardiovascular death with Avandia. FDA has not received the DREAM study data so cannot independently evaluate these data at this time. However, GSK recently received the data from McMaster University and will be submitting it soon to FDA for review.

### **The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Study**

The RECORD study is a large, ongoing, randomized, open-label trial evaluating cardiovascular outcomes in patients treated with Avandia as add-on therapy to either metformin or sulfonylurea



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in comparison to metformin and a sulfonylurea. It is a post-marketing, non-inferiority safety study of rosiglitazone vs. combined controls with a primary endpoint of cardiovascular death and hospitalization (including congestive heart failure). Cardiac events are being adjudicated in a blinded fashion to treatment assignment by a Cardiovascular Endpoints Committee.

Over 300 study centers in 25 countries in Europe are involved in the conduct of this study with each center attempting to enroll 10 to 20 patients. This non-IND study (done outside the United States and without input to the protocol or study design by the FDA) started in 2001 and completed enrollment in 2003, with over 4400 patients enrolled and proposed to be followed for 5 years. This study is still ongoing with the last patient reaching the duration of follow-up targeted in late 2008. This study has regularly been monitored by a data monitoring committee aware of the apparent elevation in cardiovascular ischemic risk from the pooled analysis. The Committee has not called for study cessation. Further, FDA has been allowed to see the results of a recent interim safety analysis and these interim data will be taken into account in FDA's considerations and actions. However, to preserve the study integrity, FDA is not explicitly commenting on these analyses.

**Next Steps for FDA**

FDA's Office of New Drugs, Office of Surveillance and Epidemiology, and Office of Biostatistics are collaborating to evaluate the data from the pooled analysis of 42 randomized clinical trials of Avandia, in the context of all other available data. As information becomes available from the continued analysis of the 42 clinical studies and from other ongoing clinical studies, FDA will communicate this information to ensure that healthcare professionals and patients have the information necessary to make appropriate therapeutic decisions. FDA will take the issue of cardiovascular risk associated with Avandia and other drugs in this pharmaceutical class to a public Advisory Committee meeting as soon as one can be convened. In the interim, healthcare professionals should factor this new information into their individual treatment decisions for their patients.



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