



DATA AFFIRMS AVANDIA (ROSIGLITAZONE MALEATE) CARDIOVASCULAR SAFETY PROFILE

Philadelphia, PA & London, UK – May 30, 2007 GlaxoSmithKline (NYSE: GSK) today confirms that a letter to the editor summarizing additional Avandia cardiovascular safety data from several large-scale clinical trials was published online today in *The Lancet*. This letter, written by Ronald L. Krall, MD, Chief Medical Officer of GlaxoSmithKline, provides the necessary context and clarifies the safety record of Avandia, which is based on sound science and backed by one of the largest research programs ever in diabetes.

Key data points include:

- The recent meta-analysis published in *New England Journal of Medicine*, which has been widely cited in media reports, omitted the total percentage number of events. The actual number of heart attacks represents a **very low frequency of events – 0.6% for both Avandia and the control group** (Avandia 86/14,371; control 72/11,634).
- Further analyses from ADOPT and DREAM – two long-term prospective clinical trials – show that the **incidence of ischemic cardiovascular events with Avandia is comparable to the two gold standard medicines** used to treat type 2 diabetes (metformin or a sulfonylurea) in the ADOPT study, and to placebo in the DREAM study.
- Findings from a soon-to-be-published study, using a **managed care database of more than 30,000 diabetes patients in a real-world setting**, show the incidence of hospitalizations for heart attack, and/or for a surgery known as revascularization for patients on **Avandia is the same as for other diabetes treatments**.
- **The independent safety monitoring board for the RECORD trial** – a large, long-term clinical trial, which has been designed to look at cardiovascular outcomes in people with diabetes – reviewed an interim analysis of cardiovascular endpoints in all study participants, and **determined that the study should be allowed to continue**.

To summarize, data from long-term, large-scale, prospective clinical trials show that the overall ischemic cardiovascular safety profile, including cardiovascular death, among diabetes patients treated with Avandia is comparable to patients treated with two other widely used diabetes medicines.

Avandia is an effective medicine that is an important treatment for millions of patients who are using it to manage their diabetes, a disease with potentially devastating consequences if left unmanaged.

Diabetes is at epidemic proportions, and GlaxoSmithKline believes that a balanced and responsible approach to assessing the risks and benefits of all available treatments is in the best interests of patients and everyone with a stake in treating this disease successfully.

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Avandia is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. *Avandia* is indicated as monotherapy and in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. *Avandia* is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycemic control.

Avandamet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate.

Avandaryl is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate.

Important Clinical Considerations When Prescribing AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin HCl) or AVANDARYL™ (rosiglitazone maleate and glimepiride)

CONTRAINDICATIONS FOR AVANDAMET:

- Renal disease or renal dysfunction (based on serum creatinine levels ≥ 1.5 mg/dL in males, ≥ 1.4 mg/dL in females)

Avandamet should not be initiated in patients ≥ 80 years of age unless creatinine clearance is normal. Temporarily discontinue *Avandamet* at the time of or prior to procedures involving intravascular iodinated contrast materials. Withhold *Avandamet* for 48 hours post procedure and reinstitute only after normal renal function has been established.

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis

Withhold therapy in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

Black Box WARNING for AVANDAMET: LACTIC ACIDOSIS

Lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during therapy with *Avandamet*

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years and may be fatal in approximately 50% of cases. Reported cases have occurred primarily in diabetic patients with significant renal

insufficiency. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. This risk may be significantly decreased by regular monitoring of renal function in patients taking *Avandamet* and by use of the minimum effective dose. Patients with congestive heart failure requiring pharmacologic management are also at increased risk of lactic acidosis.

The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Patients should be cautioned against excessive alcohol intake when taking *Avandamet*. *Avandamet* should be temporarily discontinued prior to surgical procedures, specifically those involving restricted intake of food and fluids.

CONTRAINDICATIONS FOR AVANDARYL:

- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin

CARDIAC CONSIDERATIONS:

- Rosiglitazone, like other thiazolidinediones, is associated with fluid retention (which can lead to or exacerbate heart failure) and edema
- All patients, particularly those receiving concurrent sulfonylurea or insulin therapy, those at risk for heart failure, and those with mild to moderate heart failure (New York Heart Association [NYHA] Class 1 and 2), should be monitored for signs and symptoms relating to fluid retention, including heart failure
- In addition, a higher incidence of other cardiovascular events was observed when rosiglitazone was added to insulin or when used in patients with pre-existing mild to moderate heart failure
- *Avandamet* and *Avandaryl* are not indicated for use in combination with insulin
- *Avandia*, *Avandamet*, and *Avandaryl* are not recommended in patients with NYHA Class 3 and 4 cardiac status

ADDITIONAL CARDIAC CONSIDERATIONS FOR AVANDARYL:

- The UGDP trial found that tolbutamide, a sulfonylurea, was associated with increased risk of cardiovascular mortality. Glimepiride was not studied in this trial; however, it is prudent to consider that this warning may apply to all sulfonylureas

OTHER CONSIDERATIONS:

HEPATIC:

- Check liver enzymes prior to initiation of *Avandia*, *Avandamet*, or *Avandaryl* and periodically per clinical judgment
- *Avandia*, *Avandamet*, and *Avandaryl* should not be started in patients with active liver disease or with ALT levels >2.5X the upper limit of normal
- Postmarketing reports of hepatitis and ALT >3X the upper limit of normal have been received for rosiglitazone. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established

ADDITIONAL HEPATIC CONSIDERATIONS FOR AVANDAMET:

- Since impaired hepatic function has been associated with some cases of lactic acidosis, *Avandamet* should generally be avoided in patients with clinical or laboratory evidence of hepatic disease

GENERAL:

- Postmarketing reports of new onset or worsening macular edema have been received for patients taking rosiglitazone or another thiazolidinedione. In some cases, patients' symptoms improved following discontinuation of their thiazolidinedione
- An increased incidence of bone fracture has been observed in women taking rosiglitazone. The majority of the fractures were reported in the upper arm (humerus), hand, and foot
- Anemia, hypoglycemia, resumption of ovulation, and weight gain

ADDITIONAL CONSIDERATIONS FOR AVANDARYL:

- As with all sulfonylureas, severe hypoglycemia may occur. Elderly, debilitated, or malnourished patients, or patients with adrenal, pituitary, renal, or hepatic insufficiency may be more sensitive to the glucose-lowering effect of sulfonylureas and should be started on *Avandaryl* 4 mg/1 mg. If hypoglycemia occurs, a reduction in the dose of the sulfonylurea component may be necessary.