GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
www.gsk.com

Dear Healthcare Provider:

Thank you for your inquiry regarding the potential safety issues related to AVANDIA raised in the publication of an article on May 21, 2007 in the New England Journal of Medicine (NEJM). We wanted to provide you with important information about the safety of AVANDIA® (rosiglitazone maleate).

GlaxoSmithKline disagrees with the conclusions reached in the NEJM article, which are based on incomplete evidence and a methodology that the author admits has significant limitations. The NEJM paper is based on a retrospective meta-analysis of summary information from a number of studies which is not the most rigorous way to reach definite conclusions. As the author of this meta-analysis admits: “A meta-analysis is always considered less convincing than a large, prospective trial designed to assess the outcome of interest.” Moreover, the meta-analysis published in the NEJM contradicts other published and unpublished evidence, as FDA has noted in its public alert (see the attached press release dated May 21, 2007).

As part of our ongoing pharmacovigilance program, GSK has examined data on AVANDIA from multiple sources to assess the potential risk of myocardial ischemia. These sources include our own retrospective analysis of pooled clinical trials data with AVANDIA as well as prospective clinical trials and epidemiological studies in real patient populations. The totality of the data shows that AVANDIA and traditional anti-diabetic medicines (metformin and sulfonylurea) have similar profiles related to myocardial ischemia.

In our own retrospective analysis, GSK pooled clinical trial data from double blind, randomized, controlled clinical trials of 4 and 8 mg doses of rosiglitazone. The majority of these trials were short-term, of 6 months or less in duration, and focused on evaluation of glycemic control. This post-hoc analysis of ischemic events, accounting for the duration of patient exposure, generated a hazard ratio of 1.31 (95% CI 1.01-1.70)

with an observed incidence rate of 1.99% in the rosiglitazone group and 1.51% in the control group. This observed increased risk, however, has not been confirmed in long-term randomized clinical trials or in epidemiology studies better designed to assess the safety of AVANDIA.

In ADOPT (A Diabetes Outcome Progression Trial)- one of the longest clinical trials in people with type 2 diabetes to date- GSK directly compared both the safety and effectiveness of AVANDIA with other oral anti-diabetic medicines in over 4,300 patients for up to 6 years. Data from ADOPT showed that the overall risk of serious, cardiovascular events (CV death, myocardial infarction, and stroke) for patients on Avandia was comparable to metformin and sulfonylurea (glyburide) – two of the most commonly used medicines to treat type 2 diabetes. ADOPT showed comparable rates of cardiovascular deaths. ADOPT did show a small increase in reports of myocardial infarction among the Avandia-treated group vs. metformin and vs. glyburide; however, the number of events is too small to reach a reliable conclusion. Importantly, ADOPT also demonstrated that AVANDIA maintained blood sugar control longer than metformin and sulfonylurea. Blood sugar control is a key goal in managing diabetes to help avoid long-term complications of the disease.

Furthermore, in 2000, GSK initiated RECORD- a large, long-term clinical trial prospectively designed to look at cardiovascular outcomes. The Independent Safety Monitoring Board responsible for overseeing the safety of this trial has not found in their regular operations safety risk that would interrupt continuation of the study.

Finally, a retrospective, observational analysis from a large US managed care database of 33,000 patients with Type 2 diabetes showed no difference in hospitalizations for myocardial infarction and coronary revascularization for AVANDIA-containing regimens versus other anti-diabetic agents.

Patient safety in the use of our medicines is a top priority for GSK. We have consistently shared our data on AVANDIA with the FDA and other regulatory agencies and continue to work closely with these agencies to update the AVANDIA label as appropriate so that physicians can make treatment decisions in the best interest of their patients. We have also posted our clinical trial data publicly on the company's Clinical Trial Register. GSK stands firmly behind the safety of AVANDIA when used appropriately, and we believe its significant

benefits -- as an important treatment option for physicians treating the chronic, relentlessly progressing and life threatening disease of diabetes -- outweigh treatment risks.
GSK is providing you with this information so that you can make individualized treatment decisions in the best interest of your patients. Your patients taking AVANDIA may have questions- please refer to the current Prescribing Information (PI) and Patient Information Leaflet (PIL) for AVANDIA. You may also want to refer to the PIs and PILs for AVANDAMET® (rosiglitazone maleate/ metformin HCl) and AVANDARYL™ (rosiglitazone maleate and glimepiride). GSK will also make available additional information for you to provide to your patients.

If you have additional questions or would like more information, please call the GSK Response Center at 1-888-825-5249.

Sincerely,

Alexander R. Cobitz, MD, PhD
Senior Director Metabolism
Clinical Development and Medical Affairs
GlaxoSmithKline

Please consult accompanying complete Prescribing Information and Patient Information Leaflet for AVANDIA.

FDA News

FOR IMMEDIATE RELEASE
P07-88
May 21, 2007

Media Inquiries:
Susan Cruzan, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Issues Safety Alert on Avandia

The U.S. Food and Drug Administration (FDA) is aware of a potential safety issue related to Avandia (rosiglitazone), a drug approved to treat type 2 diabetes. Safety data from controlled clinical trials have shown that there is a potentially 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, including an interim analysis of data from the RECORD trial (a large, ongoing, randomized open label trial) and unpublished reanalyses of data from DREAM (a previously conducted placebo-controlled, randomized trial) provide contradictory evidence about the risks in patients treated with Avandia.

Patients who are taking Avandia, especially those who are known to have underlying heart disease or who are at high risk of heart attack should talk to their doctor about this new information as they evaluate the available treatment options for their type 2 diabetes.

FDA's analyses of all available data are ongoing. FDA has not confirmed the clinical significance of the reported increased risk in the context of other studies. Pending questions include whether the other approved treatment from the same class of drugs, pioglitazone, has less, the same or greater risks. Furthermore, there is inherent risk associated with switching patients with diabetes from one treatment to another even in the absence of specific risks associated with particular treatments. For these reasons, FDA is not asking GlaxoSmithKline, the drug's sponsor, to take any specific action at this time. FDA is providing this emerging information to prescribers so that they, and their patients, can make individualized treatment decisions.

"FDA remains committed to assuring that doctors and patients have the latest information available to make treatment and medication use decisions. In this case, FDA is carefully weighing several complex sources of data, some of which show conflicting results, related to the risk of heart attack and heart-related deaths in patients treated with Avandia," said Steven Galson, M.D., M.P.H., director of FDA's Center for Drug Evaluation and Research. "We will complete our analyses and make the results available as soon as possible. FDA will take the issue of cardiovascular risk associated with Avandia and other drugs in this class to an Advisory Committee as soon as one can be convened."

Avandia was approved in 1999 for treatment of type 2 diabetes, a serious and life threatening disease that affects about 18 to 20 million Americans. Diabetes is a leading cause of coronary heart disease, blindness, kidney failure and limb amputation. Since the drug was approved, FDA has been monitoring several heart-related adverse events (e.g., fluid retention, edema and congestive heart failure) based on signals seen in previous controlled clinical trials of Avandia alone and in combination with other drugs, and from postmarketing reports. FDA has updated the product's labeling on several occasions to reflect these new data, most recently in 2006. The most recent labeling change for Avandia also included a new warning about a potential increase in heart attacks and heart-related chest pain in some individuals using Avandia. This new warning was based on the result of a controlled clinical trial in patients with existing congestive heart failure.

Recently, the manufacturer of Avandia provided FDA with a pooled analysis (meta analysis) of 42 randomized, controlled clinical trials in which Avandia was compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. The pooled analysis suggested that patients receiving short-term (most studies were 6-months duration) treatment with Avandia may have a 30-40 percent greater risk of heart attack and other heart-related adverse events than patients treated with placebo or other anti-diabetic therapy. These data, if confirmed, would be of significant concern since patients with diabetes are already at an increased risk of heart disease.

Avandia is manufactured by GlaxoSmithKline, which is based in Research Triangle Park, N.C.

####