Dear Prescriber:

As you may know, *Avandia* (rosiglitazone maleate) is an oral agent for the treatment of type 2 diabetes. It is indicated for use as an adjunct to diet and exercise as monotherapy or in combination with metformin or a sulfonylurea.

The labeling has been recently updated to reflect the extensive postmarketing experience of the product since its launch in June 1999. The current labeling changes also include safety information regarding the use of *Avandia* in combination with insulin, an indication for which GlaxoSmithKline (GSK) recently received an approvable letter from the Food and Drug Administration. GSK will work with the FDA to address outstanding points that must be resolved before approval for that use can be obtained. *Avandia* is not currently indicated for use in combination with insulin.

As GSK wanted to ensure that you were aware of these changes, we have enclosed a revised package insert for your review, and we have summarized the major changes to the labeling, which are as follows:

First, the prior labeling addressed the issue of thiazolidinediones, including *Avandia*, causing fluid retention and the potential for heart failure under the Precautions, Edema subsection, and discussed the use of *Avandia* in patients with New York Heart Association Class 3 and 4 status under Precautions, Use in Patients with Heart Failure subsection. The language pertaining to heart failure from these two sections has been revised and moved to a new section called "Warnings: Cardiac Failure and Other Cardiac Effects." Changes to these sections include a new warning that *Avandia* should be discontinued if any deterioration in cardiac status occurs, and a revised warning that *Avandia* is not recommended in patients with New York Heart Association Class 3 or 4 cardiac status.

While *Avandia* is not currently indicated for use in combination with insulin, the new section now also includes safety data from clinical trials evaluating combination use of *Avandia* with insulin. In these clinical trials, which included patients with long-standing diabetes (average 12 to 13 years) and a high prevalence of pre-existing medical conditions (e.g., ischemic heart disease 14%, vascular disease 9%, congestive heart failure 2.5%), an increased incidence of cardiac failure and other cardiovascular adverse events was seen in patients receiving *Avandia* and insulin compared to insulin alone. Patients who experienced heart failure in these trials were on average older, had a longer duration of diabetes and were mostly on the higher 8 mg dose of *Avandia*.

Second, the Precautions section was modified in several ways. The Precaution concerning edema was revised and a sentence added to the end of the third paragraph regarding potential issues relating to combination use with insulin. The Precaution regarding hepatic effects was revised to include postmarketing reports of adverse events. Very rarely, these reports have involved hepatic failure, with and without fatal outcome, although causality has not been established. In addition, the labeling previously included information regarding weight gain under the Clinical Pharmacology section. Information regarding weight gain, including information from the *Avandia* and insulin combination clinical trials, is now included as a separate Precaution section.

Third, the Adverse Reactions section has also been updated regarding reports of adverse events of edema and congestive heart failure seen in the insulin combination studies. In addition, that section has been updated to reflect postmarketing reports of hepatic adverse

events and events potentially related to volume expansion. Finally, the Information for Patients subsection was also updated in accordance with the other changes.

Please read the enclosed prescribing information for the full text describing these labeling changes.

GSK is confident in the safety and efficacy profile of *Avandia* based upon its extensive clinical trial experience and its widespread postmarketing use. GSK is also committed to continuing to provide valued diabetes treatment options to the millions of patients with type 2 diabetes.

If you should have any questions regarding the above information or any of our products, please contact the GSK Medical Information Department at (800) 366-8900, ext. 5231. In addition, should you need to report an adverse reaction, please do so by contacting the GSK Medical Information Department at the above number or by notifying the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.fda.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Sincerely,

Martin I. Freed, M.D.
Vice President, Metabolic Therapeutic Area
North America Medical Affairs
SmithKline Beecham, a subsidiary of the GlaxoSmithKline Group of Companies

Encl.: *Avandi*a Prescribing Information