DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021071

SAFETY LABELING CHANGE, REMS, AND PMR NOTIFICATION

SmithKline Beecham(Cork) Ltd d/b/a GlaxoSmithKline
Attention: Margaret Kreider, Ph.D.
Senior Director, Regulatory Affairs
2301 Renaissance Blvd.
Mail Code 0420
King of Prussia, PA 19406-2772

Dear Dr. Kreider:

Please refer to your new drug application (NDA) for Avandia (rosiglitazone maleate) Tablets.

Sections 505-1, 505(o)(3), and 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorize FDA to require holders of approved drug and biological product applications to develop and comply with risk evaluation and mitigation strategies (REMS), conduct postmarketing studies and clinical trials for certain purposes, and to make safety related labeling changes, based upon new safety information that becomes available after approval of the drug or biological product.

Since Avandia was approved on May 25, 1999, we have become aware of the potential for an increased risk of ischemic cardiovascular events associated with the use of rosiglitazone. This risk was most recently evaluated in a 2010 FDA meta-analysis of 52 trials, a reanalysis of existing data about cardiovascular safety, and an observational study of Centers for Medicare and Medicaid Services (CMS) data. These analyses were discussed at a July 13-14, 2010 joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. We consider this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

After considering all relevant information, as described in more detail below, we have determined that a REMS is necessary for Avandia to ensure that the benefits of the drug outweigh the risks. We are also requiring you to conduct a postmarketing study to assess a signal of a serious risk. Finally, we believe that safety related changes should be made to the labeling for Avandia[1].

[1] In accordance with section 505-1(g)(2)(C) of the FDCA, we have also determined that your approved REMS for Avandamet and Avandaryl, (NDA 021700 and 021410) must be modified based on the new safety information described in this letter. Your proposed REMS modification submission must include revising the Medication Guide and adding elements to assure safe use. The proposed REMS must be the same for all rosiglitazone products. In addition, we are requesting the same safety related changes to the labeling of these products as discussed in this letter for Avandia.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Avandia to ensure the benefits of the drug outweigh the risks of ischemic cardiovascular events.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Since Avandia already has a Medication Guide, FDA has determined that the Medication Guide must be revised to reflect the new information regarding the cardiovascular risks of Avandia, and the revised Medication Guide will become an element of the REMS.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. You must propose elements to assure safe use to meet the following goals:

- Minimize the risk of ischemic cardiovascular events by educating prescribers about the need to limit the use of Avandia to patients already taking Avandia and patients not already taking it if they are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons.
- Inform patients taking Avandia of the current state of knowledge concerning cardiovascular risk before giving them a prescription for Avandia.

Your REMS must include at least the following elements:

– Healthcare providers must be specially trained about the risks and appropriate use of Avandia and agree to:

  - Enroll in the REMS program as a prescriber of Avandia.

  - As a condition of that enrollment, attest that they will document in each patient's healthcare record at the initiation of Avandia therapy or upon writing the next prescription for Avandia that the patient is already taking Avandia or the patient is not already taking it but they are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons.

  - Enroll the patient into the Avandia REMS program

  - Provide complete risk information to each patient prescribed Avandia and document in the patient's medical record that they have received and understood the information.

– Pharmacies must be certified to dispense Avandia and agree to:

- Enroll in the Avandia REMS program as a dispenser of Avandia

- As a condition of enrollment, attest that before dispensing each prescription for Avandia they will verify: 1) that the prescriber who wrote the prescription is enrolled in the Avandia REMS program; and 2) that the patient for whom the prescription is written is enrolled in the REMS program

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be at six months, 12 months, and annually thereafter after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

In accordance with section 505-1, within 60 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to Avandia (see Appendix A). Additionally, all relevant proposed REMS materials including enrollment forms, informed consents, or educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT FOR NDA 021071
PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
PROPOSED REMS-AMENDMENT

POSTMARKETING REQUIREMENTS UNDER 505(o)

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risk of ischemic cardiovascular events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

> **1681-1:** Commission an independent re-adjudication of the results of the trial entitled, *Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes* (RECORD). Conduct the re-adjudication at the patient record level, proceeding step-wise starting with verification of the mortality findings.

Please submit timetables for final protocol submission, study completion, and submission of the final report for the study described above within 30 days of the date of this letter.

Submit the protocol to your IND 043468, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

We have received your annual report submitted on July 29, 2010, reporting on the following postmarketing requirement (PMR) communicated to you in our letter dated May 7, 2008. This trial is entitled, *Thiazolidinedione Intervention with Vitamin D Evaluation* (TIDE).

2. A randomized, prospective, controlled clinical trial to assess the effect of rosiglitazone on macrovascular events in patients with type 2 diabetes. Include at least the following three treatment groups: rosiglitazone, placebo, and pioglitazone.

You agreed to conduct this trial according to the following schedule as noted in our letter dated December 15, 2008:

Protocol Submission:	by July 31, 2008
Trial Start Date:	by February 14, 2009
Final Report Submission:	by March 31, 2014

On July 20, 2010, we notified you that this trial was being placed on partial clinical hold and could not enroll new patients, although at that time, patients already enrolled could continue treatment under the protocol. In a separate letter today, we notified you that this trial is being placed on full clinical hold. As a result, at this time, we are suspending the dates for the deliverables in this trial until further notice. If we determine that the trial cannot be completed, we will release you from the requirement to conduct the trial, or we will establish new milestones at a future date, should we determine that the PMR can and should be completed.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and discussed at the July 13-14, 2010 joint advisory committee meeting, we believe that new safety information should be included in the labeling for Avandia.

- Revise your prescribing information, including the boxed warning, and your Medication Guide to include the additional available information about the cardiovascular risks of the product and to inform prescribers and patients that Avandia should be used only in patients already taking Avandia and in patients not already taking it who are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SUPPLEMENT FOR NDA 021071
SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED.

Prominently identify subsequent submissions related to the safety labeling changes with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>> SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager in the Division of Metabolism and Endocrinology Products, at (301) 796-1306.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

ENCLOSURES:
REMS Appendices A and B

Initial REMS Approval: XX/XXXX
Most Recent Modification: XX/XXXX

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
09/23/2010