DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021071/S-039
NDA 021410/S-027
NDA 021700/S-011

SUPPLEMENTS APPROVAL

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

Dear Dr. Kreider:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received November 18, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avandia (rosiglitazone maleate) Tablets, 2 mg, 4 mg and 8 mg; Avandamet (rosiglitazone maleate/metformin hydrochloride) Tablets, 2 mg/500 mg, 4 mg/500 mg, 2 mg/1,000 mg, and 4 mg/1,000 mg; and Avandaryl (rosiglitazone maleate/glimepiride) Tablets, 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, and 8 mg/4 mg.

We acknowledge receipt of your amendments dated January 7, April 12 and 15, and May 11 and 12, 2011, to sNDA 021071/S-039, and amendments dated April 12 and 15, and May 11 and 12, 2011, to sNDAs 021410/S-027 and 021700/S-011; and your risk evaluation and mitigation strategy (REMS) assessments for NDAs 021410 and 021700 dated May 12, 2011.

These supplemental new drug applications provide for a proposed REMS for Avandia (rosiglitazone maleate) (021071/S-039), and proposed modifications to approved REMS for Avandaryl (rosiglitazone maleate/glimepiride) and Avandamet (rosiglitazone maleate/metformin hydrochloride) (021410/S-027 and 021700/S-011).

We also refer to our February 3, 2011 approval letter for sNDAs 021071/S-038, 021410/S-026, and 021700/S-010, which provided revisions to the prescribing information and Medication Guides to address the potential increased risk of ischemic cardiovascular events associated with the use of rosiglitazone as described in our September 23, 2010 Safety Labeling Change (SLC) and REMS notification letter. Our February 3, 2011 letter acknowledged receipt of sNDAs 021071/S-039, 021410/S-027, 021700/S-011 which contained your proposed REMS for Avandia (rosiglitazone maleate) and your proposed REMS modification for Avandamet (rosiglitazone maleate/metformin hydrochloride) and Avandaryl (rosiglitazone maleate/glimepiride), and notified you that the REMS would be acted on at a later date.

We have completed our review of these supplemental applications, as amended. They are **approved**, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit using the FDA automated drug registration and listing system (eLIST) the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for package inserts and text for Medication Guides), and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved with this letter be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements for Avandia (rosiglitazone maleate) were outlined in our REMS notification letter dated September 23, 2010.

Since Avandia (rosiglitazone maleate) was approved on May 25, 1999, and since the REMS for Avandamet (rosiglitazone maleate/metformin hydrochloride) and Avandaryl (rosiglitazone maleate/glimepiride) was approved on December 2, 2008, 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 considered this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

The REMS for Avandamet (rosiglitazone maleate/metformin hydrochloride) and Avandaryl (rosiglitazone maleate/glimepiride) were originally approved on December 2, 2008. The REMS consisted of a Medication Guide and a timetable for submission of assessments of the REMS. Your proposed modified REMS consists of revised Medication Guides, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Pursuant to 505-1(f)(1), we have determined that elements necessary to assure safe use are required as part of a REMS for Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin hydrochloride) and Avandaryl (rosiglitazone maleate/glimepiride) to mitigate the potential increased risk of ischemic cardiovascular events listed in the labeling. The elements to assure safe use will provide for the education of prescribers and patients so that they are aware of the risks associated with the use of rosiglitazone-containing products and about important information regarding proper patient selection and prescribing of rosiglitazone-containing products.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS for Avandia (rosiglitazone maleate), and your proposed REMS modifications for Avandamet (rosiglitazone maleate/metformin hydrochloride) and Avandaryl (rosiglitazone maleate/glimepiride), submitted on May 12, 2011, and appended to this letter, are **approved**. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of these REMS will be 6 months, 12 months, and annually thereafter, from the date of this letter.

The REMS assessment plan for all of the rosiglitazone-containing products should include, but is not limited to, the following:

1. An assessment of the extent to which the elements to assure safe use are meeting the goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goals or such elements should be modified.

2. Number of prescribers enrolled in the REMS (during the reporting period and cumulative).
3. Number of mail order/specialty pharmacies under agreement with GlaxoSmithKline for this program (during the reporting period and cumulative).
4. The number of patients enrolled and stratified by:
    - Number of patients new to therapy with rosiglitazone-containing products at time of enrollment (during the reporting period and cumulative).
    - Number of patients continuing therapy with rosiglitazone-containing products at time of enrollment (during the reporting period and cumulative).
5. The number of patients discontinued from rosiglitazone-containing products.
6. The total number of prescriptions dispensed during the reporting period for each rosiglitazone-containing product, including how many prescriptions dispensed by each mail order or specialty pharmacy.
7. Number of identified instances in which the rosiglitazone-containing products have been distributed to mail order/specialty pharmacies not under agreement with GlaxoSmithKline (during the reporting period and cumulative).
8. Number of mail order/specialty pharmacies that dispense rosiglitazone-containing products to patients who are not enrolled in the program, and number of instances of this type of unauthorized dispensing for individual mail-order pharmacies (during the reporting period and cumulative).
9. Number of mail order/specialty pharmacies that dispense rosiglitazone-containing products using a prescription written by a prescriber who is not enrolled in the program, and number of instances of this type of unauthorized dispensing for individual specific mail order/specialty pharmacies (during the reporting period and cumulative).
10. Number of prescribers who are not enrolled in the program and who wrote one or more prescriptions for rosiglitazone-containing products, and number of prescriptions written by each un-enrolled prescriber (during the reporting period and cumulative).
11. Number of enrolled prescribers who wrote a prescription for a patient not yet enrolled and number of instances in which this occurred by prescriber (during the reporting period and cumulative).
12. Number of prescribers de-enrolled from the program for non-compliance (during the reporting period and cumulative).
13. The results of surveys to ascertain prescribers' and patients' understanding about the safe use of rosiglitazone-containing products.
14. A metric of whether or not all dispensing in the U.S. is occurring under the REMS ETASU. This should include the amount of drug product dispensed in the U.S. and the amount accounted for by the ETASU processes. The assessment plan should include utilization data as collected via REMS enrollment forms/verifications and independently from sales data and/or independent vendors. Explain the utilization data to be submitted as part of the REMS assessment reports.
15. With regard to the communication plan:
    - The date of launch of the communication plan (Dear Healthcare Provider letter and Dear Pharmacist letter)
    - The number of recipients of the Dear Healthcare Provider letter distribution

- The number of recipients of the Dear Pharmacist letter distribution
- Date(s) of distribution of the Dear Healthcare Provider letter
- Date(s) of distribution of the Dear Pharmacist letter
- A copy of all documents included in each distribution

16. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
17. Information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Each of the items above will be included in each assessment report with the exception of the results of surveys to ascertain prescribers' and patients' understanding about the safe use of rosiglitazone-containing products. Results of surveys to ascertain prescribers' and patients' understanding about the safe use of rosiglitazone-containing products need not be included in the first assessment report submitted, but should be included in all subsequent assessment reports.

We remind you to submit the survey methodology and survey instruments used to assess program understanding for FDA review at least 90 days before the evaluation using the survey is conducted.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

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

NDA 021071, 021410, and 021700 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021071, 021410, and 021700
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021071, 021410, and 021700
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling.

To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug products must be promptly revised to be consistent with the labeling changes approved in these supplements, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
- Content of Labeling (3)
- Medication Guides (3)
- REMS (3)
- REMS Materials (3)

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

/s/

MARY H PARKS
05/18/2011