DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21071/S-041
NDA 21410/S-030
NDA 21700/S-013

SUPPLEMENT APPROVAL
REMOVE REMS ELEMENT

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 Supplemental New Drug Applications (sNDAs) dated and received November 16, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AVANDIA (rosiglitazone maleate) Tablets, AVANDARYL (rosiglitazone maleate and glimepiride) Tablets, and AVANDAMET (rosiglitazone maleate and metformin hydrochloride) Tablets.

We acknowledge receipt of your amendments dated January 18 and May 10, 2012. We also acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment contained in the submissions dated November 16, 2011. After consultation between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have found the REMS assessment to be complete, as stated in our letter dated January 12, 2012.

These supplemental new drug applications propose modifications to the approved REMS for AVANDIA (rosiglitazone maleate) Tablets, AVANDARYL (rosiglitazone maleate and glimepiride) Tablets, and AVANDAMET (rosiglitazone maleate and metformin hydrochloride), and propose to eliminate the requirement for the approved communication plan as an element of the approved REMS.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for AVANDIA (rosiglitazone maleate) was originally approved on May 18, 2011; the REMS for AVANDAMET (rosiglitazone maleate and metformin hydrochloride) and AVANDARYL (rosiglitazone maleate and glimepiride) were originally approved on December 2, 2008. The most recent REMS modification for all three rosiglitazone-containing products was approved on November 13, 2011. 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.

Your proposed modification to the REMS consists of additions to the patient enrollment form to facilitate processing and tracking, the addition of a new patient enrollment form for Veterans Administration (VA) patients to accommodate the unique processes and requirements of the VA, and a request to eliminate the requirement for the communication plan as an element of the REMS.

Because the November 16, 2011, REMS assessment demonstrates that the communication plan has been completed, after consultation between OND and OSE, we have determined that it is no longer necessary to include the communication plan as an element of the approved REMS to ensure that the benefits of the drug outweigh the risks.

We agree with your proposed modifications to the REMS for AVANDIA (rosiglitazone maleate), AVANDAMET (rosiglitazone maleate and metformin hydrochloride) and AVANDARYL (rosiglitazone maleate and glimepiride).

Your proposed modified REMS, submitted on May 10, 2012, and appended to this letter, is approved. The modified REMS consists of a Medication Guide, 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 the REMS will remain the same as that approved on May 18, 2011.

The revised REMS assessment plan 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 evaluate 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. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

16. 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.

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 the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021071/ NDA 021410/ NDA 021700 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic REMS submission.

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

NDA 021071/ NDA 021410/ NDA 021700 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021071/ NDA 021410/ NDA 021700
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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

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

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 contact Jena Weber, Regulatory Project Manager, at (301) 796-1306.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

ENCLOSURE: REMS

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

/s/

AMY G EGAN
05/30/2012