



NDA 021410/S-036
NDA 021410/S-037
NDA 021410/S-038

**SUPPLEMENT APPROVALS
REMOVE REMS ELEMENT**

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

Dear Dr. Kreider:

Please refer to your Supplemental New Drug Applications (sNDAs), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA):

NDA Number	Supplement Number	Product Name	Date of Submission	Date of Receipt
021410	036	Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets	July 1, 2013	July 1, 2013
	037		January 20, 2014	January 22, 2014
	038		January 22, 2014	January 22, 2014

We acknowledge receipt of your amendments dated August 23, 2013 (S-036), September 30, 2013 (S-036), December 20, 2013 (S-036), February 12, 2014 (S-037), March 4, 2014 (S-038), March 31, 2014 (S-038), April 14, 2014 (S-038) and April 29, 2014 (S-038), and your risk evaluation and mitigation strategy (REMS) assessments dated July 1, 2013 and January 22, 2014. We also acknowledge receipt of your email dated April 11, 2014, which included the final, agreed-upon labeling. The submission dated April 29, 2014 contained the final risk evaluation and mitigation strategy (REMS) documents.

The "Prior Approval" supplemental new drug application S-036 proposes to add a contraindication for use in patients with a history of hypersensitivity reaction to rosiglitazone or any of the inactive ingredients.

We also refer to our letter dated November 25, 2013, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for rosiglitazone products. This information pertains to the readjudicated results of the

Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial.

The “Prior Approval” supplemental new drug applications S-037 and S-038 provide for revisions to the labeling for Avandamet (rosiglitazone maleate and metformin hydrochloride), and propose modifications to the approved Rosiglitazone REMS Program, consistent with our November 25, 2013, Safety Labeling Change Notification and REMS Modification Notification letter.

APPROVAL & LABELING

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 and with the minor editorial revisions indicated in the enclosed labeling.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as 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 that includes labeling changes 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, as well as annual reportable changes and annotate each change. 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 today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS with elements to assure safe use for Avandamet was originally approved on May 18, 2011, and the most recent REMS modification was approved on September 16, 2013. The single, shared system REMS program for rosiglitazone-containing medicines, the Rosiglitazone REMS Program was approved on January 25, 2013, and the most recent REMS modification was approved on September 16, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of the changes outlined in the November 25, 2013 letter, including removal of the Medication Guide as an element of the REMS and modification of the elements to assure safe use.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of the Avandamet outweigh the risks. We remind you that the Medication Guide will continue to be part of the approved labeling for Avandamet in accordance with 21 CFR 208.

We have also determined that elements to assure safe use that require that healthcare providers who prescribe rosiglitazone for outpatient or long-term care use are specially certified, that rosiglitazone be dispensed only by specially certified pharmacies, and that rosiglitazone be dispensed only to patients with evidence or other documentation of safe use conditions are no longer necessary to ensure the benefits of the drug outweigh the risks.

Your proposed modified REMS, submitted on April 29, 2014, and appended to this letter, is approved.

The modified REMS consists of elements to assure safe use to provide training on the current state of knowledge concerning the cardiovascular risk of rosiglitazone-containing medicines to health care providers who are likely to prescribe rosiglitazone-containing medicines and a timetable for submission of assessments of the REMS.

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.

The timetable for submission of assessments of the REMS will remain the same as that approved on May 18, 2011.

At least 24 hours prior to issuing the Dear Healthcare Provider letter(s) that are required as part of the REMS, please submit an electronic copy of the letter to this NDA, and to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

The revised REMS assessment plan should include, but is not limited to, the following:

- Total number of letters sent to prescribers
- Total number of letters returned, i.e. not received by prescribers
- Total number of letters sent to Professional Society Leaders
 - Results of follow-up with Professional Society leaders regarding the disposition of the letters
 - the number and names of Professional Societies that acknowledged receipt of letter
 - the number and names of Professional Societies that conveyed the information from the letter to members
 - the number and names of Professional Societies that did not convey the information from the letter to members
 - reasons the information was not conveyed to members
- Number of emails sent to prescribers previously enrolled in the Rosiglitazone REMS Program
 - Number of these prescribers for which returned receipt (opened email notification) is not received
- Number of visits to access the training materials by self-identified prescribers for the reporting period.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved

strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

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 the 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 021410 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 drug 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 021410 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 021410
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021410
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
Office of Prescription Drug Promotion (OPDP)
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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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, call Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
REMS

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

/s/

JEAN-MARC P GUETTIER
05/07/2014