DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-842/S-011
NDA 22-024

SUPPLEMENT APPROVAL
REMS NOTIFICATION

Takeda Global Research & Development Center, Inc.
Attention: Sandra Cosner, R.Ph.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045

Dear Ms. Cosner:

Please refer to your new drug application (NDA) for ACTOPLUS MET (pioglitazone HCl + metformin HCl) fixed-dose combination tablets, 15 mg/500 mg and 15 mg/850 mg (NDA 21-842) and ACTOPLUS MET XR (pioglitazone HCl + metformin HCl extended release) Tablets 15 mg/1000mg and 30mg/1000mg (NDA 22-024).

Please also refer to you supplemental new drug application dated September 16, 2009, received September 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ACTOPLUS MET (pioglitazone HCl + metformin HCl) fixed-dose combination tablets (NDA 21-842/S-011).

This supplemental new drug application provides for revisions to the approved Medication Guide, a proposed modification to the approved Risk Evaluation and Mitigation Strategy (REMS) for ACTOPLUS MET (pioglitazone HCl + metformin HCl), and a REMS assessment.

The REMS for ACTOPLUS MET (pioglitazone HCl + metformin HCl) was approved on September 14, 2009, under NDA 21-842/S-009. The REMS consists of a Medication Guide that was approved for both ACTOPLUS MET (pioglitazone HCl + metformin HCl) and ACTOPLUS MET XR (pioglitazone HCl + metformin HCl extended release) and a timetable for submission of assessments of the REMS. The proposed modified REMS for ACTOPLUS MET (pioglitazone HCl + metformin HCl) contains a Medication Guide modified to delete all references to the ACTOPLUS MET XR (pioglitazone HCl + metformin HCl extended release) product as this product is not currently marketed. The Medication Guide is otherwise unchanged and will serve as a stand alone Medication Guide for the ACTOPLUS MET (pioglitazone HCl + metformin HCl) product.

We have completed our review of this application, NDA 21-842/S-011, and it is approved, effective on the date of this letter. Your modified REMS is appended to this letter. The timetable for submission of assessments and your REMS assessment plan will remain the same as that approved on September 14, 2009, with the original approval of the REMS.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-842/S-011**".

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

A REMS was approved on May 12, 2009 for ACTOPLUS MET XR (pioglitazone HCl + metformin HCl extended release). The REMS consists of a Medication Guide that was approved for both ACTOPLUS MET (pioglitazone HCl + metformin HCl) and ACTOPLUS MET XR (pioglitazone HCl + metformin HCl extended release) and a timetable for submission of assessments of the REMS. For REMS purposes, we are treating your September 16, 2009 submission as a proposed modification to the REMS under section 505-1(g)(1) of the FDCA to revise the Medication Guide for ACTOPLUS MET XR (pioglitazone HCl + metformin HCl extended release to delete all references to ACTOPLUS MET (pioglitazone HCl + metformin HCl). Accordingly, Takeda must submit a new proposed modified REMS in a prior approval supplement (PA) that includes a revised Medication Guide.

Your proposed REMS modification submission should include the REMS document that was approved on May 12, 2009, in addition to your revised Medication Guide. The timetable for submission of assessments of the REMS may remain the same as that approved on May 12, 2009.

In accordance with section 505-1, proposed modifications to an approved REMS must be accompanied by an assessment of that REMS. The assessment of this REMS may consist of a statement that the Medication Guide plan would be adequate with the proposed modifications to achieve its purpose.

We request that you submit your proposed modified REMS and REMS assessment as described above to this NDA within 30 days of the date of this letter. The REMS assessment and the proposed modified REMS should be included in the same submission. The modified REMS, once approved, will create enforceable obligations.

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

NEW SUPPLEMENT FOR NDA 21-842
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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

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

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

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 & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Medication Guide
REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21842	SUPPL-11	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ACTOPLUS-MET (METFORMIN/PIOGLITAZONE HCL

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
10/21/2009