



NDA 21-842/S-009

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 supplemental new drug application dated September 5, 2008, received September 8, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ACTOPLUS MET (pioglitazone HCl plus metformin HCl) tablets, 15 mg/500mg and 15 mg/850 mg.

We acknowledge receipt of your submissions dated October 6 and 20, 2008, and May 15, and July 2, 2009.

This Prior Approval supplemental new drug application provides for the conversion of the approved patient package insert to a Medication Guide, revisions to the carton and container labels, in addition to a proposed REMS.

We have completed our review of this application, as amended. This application is **approved**, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the Medication Guide). 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-009.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels (submitted on July 2, 2009) as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-842/S-009.**" Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, And Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (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)).

Since ActoPlus Met was approved on August 29, 2005, we have become aware of reports of congestive heart failure in patients being treated with pioglitazone-containing products in both the clinical trial and post-marketing setting. This information was not available when ActoPlus Met was approved. We consider this information to be “new safety information” as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ActoPlus Met poses a serious and significant public health concern requiring the distribution of a Medication Guide.

The Medication Guide is necessary for patients’ safe and effective use of ActoPlus Met. FDA has determined that ActoPlus Met is a product for which patient labeling could help prevent serious adverse effects. FDA has also determined that ActoPlus Met has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients’ decisions to use, or continue to use ActoPlus Met. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed ActoPlus Met.

Your proposed REMS, submitted on October 6, 2008, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

Your assessment of the REMS should include an evaluation of:

- a. Patients’ understanding of the serious risks of ActoPlus Met
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. 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 updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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.

Prominently identify the submission containing 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:

NDA 21-842 REMS ASSESSMENT

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

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21-842
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

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

REPORTING REQUIREMENTS

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

HEALTH CARE PROFESSIONAL LETTER

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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, carton and container labels

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21842

SUPPL-9

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
09/14/2009