DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22024/S-002 **SUPPLEMENT APPROVAL**

Takeda Global Research & Development Center, Inc.
Attention: Jessica Y. Lee, Ph.D.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Lee:

Please refer to your supplemental new drug application (sNDA) dated November 19, 2009, received November 20, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ACTOPLUS MET XR (pioglitazone hydrochloride + metformin hydrochloride extended-release) fixed-dose combination tablets, 15 mg/1000 mg and 30 mg/1000 mg.

We acknowledge receipt of your amendments dated April 16, 2010, and December 3 and 9, 2010; and your risk evaluation and mitigation strategy (REMS) assessment dated November 19, 2010.

This supplemental new drug application provides for a proposed modification to the approved REMS for ACTOPLUS MET XR (pioglitazone hydrochloride + metformin hydrochloride extended release).

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

We note that your December 3, 2010, submission includes final printed labeling (FPL) for your Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and text for the Medication Guide) 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.

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for ACTOPLUS MET XR (pioglitazone hydrochloride + metformin hydrochloride extended release) was originally approved on May 12, 2009. The REMS consists of a Medication Guide, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a stand-alone Medication Guide for ACTOPLUS MET XR which will replace the combination Medication Guide that was originally approved for both ACTOPLUS MET (pioglitazone hydrochloride + metformin hydrochloride) and ACTOPLUS MET XR. A stand-alone Medication Guide and REMS modification were previously approved for ACTOPLUS MET on October 21, 2009.

Your proposed modified REMS, submitted on December 9, 2010, and appended to this letter, is approved. The timetable for submission of assessments of the REMS and your REMS assessment plan will remain the same as that approved on May 12, 2009.

We remind you that assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), 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.

We also 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.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your 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 as appropriate:

NDA 22024 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22024
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22024
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

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

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:
Medication Guide (updated)
REMS
Package insert (no changes with this supplement, version approved May 12, 2009, under original NDA 022024)

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
12/22/2010