DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021842/S-008
NDA 021842/S-010

SUPPLEMENTS APPROVAL

Takeda Global Research & Development Center, Inc.
Attention: Jessie 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) for supplement 008 dated August 25, 2008, received August 26, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Actoplus Met (pioglitazone hydrochloride plus metformin hydrochloride) Tablets, 15 mg/500 mg and 15 mg/850 mg.

We acknowledge receipt of your amendments dated February 23, and April 16, 2009, and April 29, August 16, September 13, and December 14, 2011, and February 3 and 15, and April 24, 2012. Your risk evaluation and mitigation strategy (REMS) assessment was submitted on April 29, 2011.

We also refer to supplement 010 dated May 29, 2009, received June 1, 2009, and to your amendments dated June 22, July 29, and August 26, 2009, and April 19, 2010, and May 12, August 17, September 13 and 14, and December 14, 2011, and February 3 and 15, and April 24 and 26, 2012.

These "Prior Approval" supplemental new drug applications provide for:

S-008: the conversion of the package insert into Physician Labeling Rule (PLR) format, and a proposed modification to the approved REMS.

S-010: labeling changes based on results from clinical study 01-06-TL-OPIMET-008 entitled, "A Phase 3b, Double-Blind, Randomized Study to Determine the Efficacy and Safety of Pioglitazone HCI and Metformin HCI Fixed-Dose Combination Therapy Compared to Pioglitazone HCI Monotherapy and Metformin HCI Monotherapy in the Treatment of Subjects with Type 2 Diabetes."

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.

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.

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 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 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 these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, 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 numbers 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Actoplus Met (pioglitazone hydrochloride and metformin hydrochloride) was originally approved on September 14, 2009, and REMS modifications were approved on October 21, 2009, and August 4, 2011. 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 revisions to the Medication Guide to include information about the risk of congestive heart failure in patients being treated with Actoplus Met (pioglitazone hydrochloride and metformin hydrochloride) that is consistent with the revised language in the PLR package insert.

Your proposed modified REMS, submitted on February 3, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on August 4, 2011.

There are no changes to the REMS assessment plan described in our September 14, 2009, letter.

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 postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval 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 021842 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 021842 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021842
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 021842
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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert, 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/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), 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, 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

ENCLOSURES:
Package Insert
Medication Guide
REMS

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
05/17/2012