



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Silver Spring MD 20993

NDA 022024/S-012

NDA 022024/S-013

**SUPPLEMENT APPROVAL**

Takeda Pharmaceutical U.S.A., Inc.  
Attention: Esha Desai, MS, RAC (US, EU)  
Manager, Global Regulatory Affairs Development  
One Takeda Parkway  
Deerfield, IL 60015

Dear Ms. Desai:

Please refer to your Supplemental New Drug Applications (sNDAs) and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ActoPlus Met XR (pioglitazone and metformin hydrochloride extended release) tablets.

**Supplement 012**

This Prior Approval sNDA, dated and received July 30, 2015, provides for updates to the Warnings and Precautions section of the package insert (PI) to include information on bladder cancer risk based on additional information from a 10-year study and changes to the PI to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

**Supplement 013**

We also refer to our letter dated April 8, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling. This information pertains to the lower risk of lactic acidosis in certain patients with renal impairment who use products containing metformin.

This Changes Being Effected sNDA, dated and received May 5, 2016, provides for revisions to the labeling for ActoPlus Met XR consistent with our April 8, 2016, letter and the changes agreed upon in our October 3, 2016, correspondence.

**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 listed below and indicated in the enclosed labeling.

- The revision date listed for the Highlights of Prescribing Information was updated to reflect the date of approval of these supplements.
- The revision date listed for Recent Major Changes, Urinary Bladder Tumors, was updated to reflect the date of approval of these supplements.

## **WAIVER OF HIGHLIGHTS SECTION**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

## **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 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 via 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 with the revisions indicated above 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).

## **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 applications, you are exempt from this requirement.

## **FULFILLMENT OF POSTMARKETING REQUIREMENT**

We have received your submission dated August 28, 2014, containing the final report for the following postmarketing requirement listed in the August 4, 2011, approval letter for sNDA 022024/S-007:

- 1783-1 Continuation and modification of your ten-year epidemiological study assessing whether treatment with pioglitazone hydrochloride is associated with an increased risk of bladder cancer in men and women with diabetes.

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all of your postmarketing requirements acknowledged in our August 4, 2011, letter.

## **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:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available

at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **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 Liz Godwin, Regulatory Project Manager, at (240) 402-3438.

Sincerely,

*{See appended electronic signature page}*

Jennifer Rodriguez Pippins, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:

Content of Labeling

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

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/s/

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JENNIFER R PIPPINS

12/12/2016