DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-024

NDA APPROVAL

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

Dear Ms. Cosner:

Please refer to your new drug application (NDA) dated March 31, 2006, received April 3, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ACTOPLUS MET XR (pioglitazone hydrochloride and metformin hydrochloride extended-release) fixed-dose combination tablets, 15 mg/1000 mg and 30 mg/1000 mg.

We acknowledge receipt of your submissions dated February 6, 2007, and February 29, April 30, May 9, October 7 (2 submissions), 16, and 28, November 24, and December 10, 2008, and February 11, March 11, and 25, and April 1, 2009.

The April 30, 2008, submission constituted a complete response to our February 2, 2007, action letter.

ACTOPLUS MET XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with pioglitazone and metformin or who have inadequate glycemic control on pioglitazone alone or metformin alone.

We have completed our review of this application, as amended. It is **approved**, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text (text for the package insert and Medication Guide submitted March 25, 2009, and carton and container labels submitted December 10, 2008).

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 labeling (text for the package insert and 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 22-024."**

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 10, 2008, submission containing printed carton and container labels. Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels 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).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-024**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are granting a full waiver for the pediatric study requirement citing safety concerns with pioglitazone hydrochloride, one of the active ingredients in ACTOPLUS MET XR, in the pediatric population.

RISK EVALUTION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

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 XR 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 XR.

FDA has determined that ACTOPLUS MET XR is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use ACTOPLUS MET XR. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed ACTOPLUS MET XR.

Your proposed REMS, appended to this letter, submitted on October 16, 2008, is **approved**. The REMS consists of the Medication Guide included with this letter and the 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 XR
b. A report on periodic assessments of the distribution and dispending 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

Prominently identify submissions containing REMS assessments or proposed REMS modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-024 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-024
PROPOSED REMS MODIFICATION
<other supplement identification> [if included]
<REMS ASSESSMENT> [if included]

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

Reference is made to your amendments dated October 20, 2008, to NDA 21-073 for Actos (pioglitazone) Tablets, and to NDA 21-925 for Duetact (pioglitazone/glimepiride fixed-dose combination) Tablets, which contain a proposed Medication Guide and REMS. These amendments are under review.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert, Medication Guide, REMS, Carton Labels, Container Labels

---

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

/s/

Mary Parks

5/12/2009 09:12:37 PM