CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-024

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-024

Takeda Global Research & Development Center, Inc.
Attention: Sandra Cosner, R.Ph.
Program Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

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 for ACTOPLUS MET™ XR (pioglitazone HCl/metformin HCl extended-release) fixed-dose combination tablets, 15 mg/1000 mg and 30 mg/1000 mg.

We acknowledge receipt of your submissions dated June 30, October 17, November 3 and 30, and December 20, 2006, and January 29, 2007.

We completed our review of this application and it is **approvable**. Before the application may be approved, it will be necessary for you to correct the deficiencies cited by our investigator during a recent inspection of the drug product (metformin HCl) manufacturing facility at Andrx Pharmaceuticals, Inc.(4955 Orange Drive, Ft. Lauderdale, FL 33314), for this application. Our field investigator conveyed deficiencies to the facility representative. Satisfactory resolution to these deficiencies is required before this application may be approved.

In addition, it will be necessary for you to submit revised draft labeling that addresses the general comment and includes changes to the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics and Drug Metabolism, Absorption and Bioavailability** subsection summarized below.

General Comment:

> You have proposed one set of prescribing information for both ACTOPLUS MET™ and ACTOPLUS MET™ XR. Two doses of ACTOPLUS MET™ XR are proposed: pioglitazone/metformin extended-release 15 mg/1000 mg and 30 mg/1000 mg. The usual maximum recommended dose of pioglitazone is 45 mg given once daily, while the maximum daily dose of metformin is 2000 mg. This information should be clearly stated in the **DOSING and ADMINISTRATION** section. You also propose that either dose of ACTOPLUS MET XR may be used as the initial dose; a titrated maximal dose should be stated in the prescribing information.

The different doses of pioglitazone and metformin in ACTOPLUS MET™ and ACTOPLUS MET™ XR should be highlighted. ACTOPLUS MET™ tablets contain pioglitazone/metformin 15 mg/500 mg and 15 mg/850 mg, while ACTOPLUS MET™ XR tablets consist of pioglitazone/metformin XR 15 mg/1000 mg and 30 mg/1000 mg.

Under the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics and Drug Metabolism, Absorption and Bioavailability** subsection, the following changes need to be made (underline indicates new language inserted and ~~strikethrough~~ indicates deletion of language:

"Time to peak serum concentration was prolonged by approximately 3 and 2 hours respectively for (b)(4) pioglitazone and metformin under fed conditions."

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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
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