CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-024

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO

Completed May 1, 2009

Hylton V. Joffe, M.D., M.M.Sc.

NDA: 22-024
Sponsor: Takeda
Drug: Actoplus Met XR (pioglitazone plus extended-release metformin fixed dose combination tablets)

Proposed Indication: 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

Primary Medical Reviewers: Joanna Zawadzki, M.D.
Karen M. Mahoney, M.D.

Actoplus Met XR is a fixed-dose combination tablet consisting of pioglitazone and extended-release metformin that permits once daily dosing. The new drug application (NDA) for Actoplus Met XR was submitted on June 30, 2006. The Division issued an approvable letter because of deficiencies at the manufacturing facility where the metformin component is produced.

Takeda has subsequently submitted a complete response to the approvable letter, which is the subject of this memorandum. Please see Dr. Karen Mahoney's acting clinical team leader memorandum, dated November 28, 2008, which is attached to this document as an appendix and which summarizes the pertinent findings from the discipline reviews of the complete response.

As mentioned by Dr. Mahoney, the manufacturing deficiencies have been rectified. Dr. Mahoney also discusses the revisions to the package insert and the implementation of Risk Evaluation and Mitigation Strategies (REMS) with a medication guide for the boxed warning of heart failure.

The Division and the sponsor have reached agreement on the wording for the package insert and medication guide (see finalized label and medication guide that will be appended to the approval letter for this NDA). Of note, the Pediatric Review Committee (PeRC) agreed with the Division's plan to grant a full waiver for this product (email communication from Mr. George Greeley, dated January 8, 2009) but requested additional language in the "Pediatric Use" section of the package insert explaining why Actoplus Met XR is not recommended for use in children.

The current memo will address all outstanding issues that had not yet been resolved at the time of Dr. Mahoney's review.

1. The pediatric text has been revised to explain why Actoplus Met XR is not recommended for use in children. The revised text states "Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data. Risks including fractures and other adverse effects associated with pioglitazone, one of the components of ACTOPLUS MET and ACTOPLUS MET XR, have not been determined in this population (see **WARNINGS** and **PRECAUTIONS**)."

2. The Medication Guide now includes the following statement pertaining to bladder cancer listed under "What are other possible side effects of ACTOPLUS MET and ACTOPLUS MET XR?": "In studies of pioglitazone (one of the medicines in ACTOPLUS MET and ACTOPLUS MET XR), bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone."

3. The Division of Medication Error Prevention and Analysis (DMEPA) requested revisions to the proposed container labels and carton labeling to decrease the potential for selection errors and to increase readability. The sponsor revised these labels accordingly, and DMEPA agreed with the revisions (see review of Jinhee Lee, Pharm.D., December 17, 2008).

4. The draft approval letter, including the FDA Amendments Act (FDAAA) language regarding REMS and labeling were reviewed and cleared by the Safety Requirements Team.

5. The Actoplus Met XR tradename was re-evaluated during this review cycle and determined to be acceptable (see review of Ms. Cathy Miller).

Recommendation: The Actoplus Met XR NDA can be approved.

REVIEW MEMORANDUM

28 Nov 08

Karen Murry Mahoney, MD, FACE
Acting Diabetes Team Leader, Division of Metabolism and Endocrinology Products (DMEP)

Re: Clinical Review of Full Prescribing Information and Medication Guide for NDA 22024 ActoPlus Met XR® (pioglitazone hydrochloride and metformin hydrochloride, fixed-dose combination tablets, extended release formulation)

The previous reviewer for this application was unable to complete the review, and therefore a memorandum by the acting team leader is being entered.

On 30 Jun 2006, Takeda Global Research and Development submitted NDA 22024, for an extended release formulation of ActoPlus Met XR®, hereafter referred to as APMX. This was submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, and consisted of two bioequivalence studies, a food effect study, and information on Chemistry, Manufacturing and Controls. Clinical Pharmacology review concluded that the bioequivalence and food effect studies were adequate, but a field inspection identified deficiencies at the manufacturing facility at Andrx Pharmaceuticals, where the metformin component of the combination product is produced. On 2 Feb 2007, DMEP issued an approvable letter, citing the following deficiencies:

> 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) pioglitazone and metformin under fed conditions."

Please see Dr. Chien-Hua Niu's Chemistry, Manufacturing and Controls review memo. On 30 Oct 2008, the Office of Compliance provided confirmation that a repeat Establishment Evaluation (inspection) had been performed, and the previously identified deficiencies had been corrected.

Dr. Jaya Vaidyanathan, the Clinical Pharmacology reviewer, has confirmed that edits to the Full Prescribing Information (FPI) adequately address the deficiencies noted in the approvable letter.

On 14 Aug 2007, a Boxed Warning regarding heart failure risk had been added to the Full Prescribing Information for Actos® (pioglitazone hydrochloride). This Boxed Warning is also required for the APMX label, and in discussions with the DMEP Safety Team, and the Safety Requirements Team of the Office of New Drugs in the Center for Drug Evaluation and Research, it was determined that this Boxed Warning necessitated a Patient Medication Guide (Med Guide) for pioglitazone-containing products.

This memo documents the significant changes to the APMX FPI, and discusses the Med Guide language.

Changes to the Full Prescribing Information:

- A Boxed Warning for heart failure has been added to the beginning of the FPI. It is identical to that approved for Actos® (pioglitazone hydrochloride).
- The previous Boxed Warning for lactic acidosis has been moved to the beginning of the label. Boxed Warnings are to be placed at the beginning of labels, and this is consistent with other metformin-containing combination products. The language of the lactic acidosis Boxed Warning has been edited to be consistent with that of other metformin-containing products.
- In the DESCRIPTION section, and in the CLINICAL PHARMACOLOGY section (Pharmacokinetics and Drug Metabolism, Absorption and Bioavailability subsection) language has been added to clarify the differences between the ActoPlus Met immediate release formulation, and the APMX extended release formulation.
- The different doses of pioglitazone and metformin in the immediate release and extended release formulations are now clarified in tabular form.
- The requested statement regarding the time to peak concentration under fed conditions has been added.

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