

**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.

- Information on gemfibrozil and rifampin drug-drug interaction studies have been added, consistent with interim additions to the Actos® label.
- Consistent with the Actos® label, a contraindication has been added for initiation of ActoPlus Met (APM) or APMX in patients with New York Heart Association functional Class III or IV heart failure.
- In the WARNINGS section, language regarding heart failure has been added, again consistent with the Actos® label.
- In the PRECAUTIONS section, a statement has been added that there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with APM, APMX, or any other anti-diabetic drug. This statement is in the label of all oral agents used to treat type 2 diabetes mellitus.
- Also in the PRECAUTIONS section, information has been added regarding macular edema and fractures, consistent with recent additions to the Actos® label.
- Information on bladder cancer in clinical trials has been added, also consistent with recent additions to the Actos® label.
- Cardiovascular safety data from the PROactive trial have been added, consistent with the Actos® label.
- The DOSAGE AND ADMINISTRATION section has been augmented to clarify dosing differences for APM and APMX.
- Under the Special Populations subsection, statements have been added that APM and APMX should only be used in patients with normal renal function, and that use in children is not recommended.

Medication Guide Language:

Please see the clinical review of the Medication Guide for Avandamet® (rosiglitazone maleate and metformin hydrochloride, NDA 21410, supplement 025, Division File System archive 1 Aug 08). This APMX Medication Guide strongly parallels that for Avandamet®, except that information regarding the safety signal for myocardial ischemic events with rosiglitazone has been omitted.

The Medication Guide emphasizes patient information regarding heart failure and lactic acidosis. As with the Avandamet® med guide, the APMX med guide information regarding lactic acidosis has been modified to make it more useful to patients in helping them to avoid the conditions under which lactic acidosis occurs, because most cases of lactic acidosis can be avoided if the drug is taken properly.

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/s/

Karen Mahoney
11/28/2008 01:14:22 PM
MEDICAL OFFICER
Acting Diabetes Team Leader

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/s/

Hylton Joffe
5/1/2009 11:17:32 AM
MEDICAL OFFICER

Mary Parks
5/1/2009 03:24:35 PM
MEDICAL OFFICER
Concur w/ Dr. Joffe's recommendations

MEDICAL OFFICER REVIEW

Division of Metabolism and Endocrinology Products (HFD-510)

Application #:NDA 22-024

Application Type:

**Commercial NDA 505 (b)(2)
Dated 3/31/06**

Electronic submission

[\\Cdseesub1\n22024\N_000\2006-03-31](#)

Sponsor:Takeda Global Research & Development Center, Inc. (TGRD)

Proprietary Name:

**ACTOPLUS MET™ XR
Fixed-dose combination tablet
ACTOS® (pioglitazone HCl)
NDA 21-073 Takeda Pharm. N.A.
FORTAMET® (metformin HCl
extended release) NDA-21-574 Andrx
Labs, LLC
[also called AD-4833XT]**

Pharmaceutical3031400

Category:Fixed-dose combination
Peroxisome proliferator-activated
receptor (PPAR) α γ agonist or
Thiazolidinedione +
Biguanide

Route of Administration: oral

Indication: (b) (4)

Dosage: Pioglitazone/metformin
15 mg/1000 mg
30 mg/1000 mg

Related Application: ACTOPLUS MET (Takeda)
(NDA 21-842 approved 8/29/05)
pioglitazone/metformin fixed-dose
tablets) 15mg/500mg and 15mg/850mg

Date Review Completed: January 12, 2007

Reviewer:Joanna K. Zawadzki, M.D.

REVIEW SUMMARY:

See review.

OUTSTANDING ISSUES: Please see labeling comments to minimize possible confusion between ACTOPLUS MET XR and ACTOPLUS MET, both for clinicians and patients. The labeling comments should be forwarded to the sponsor. The sponsor's submitted prescribing information is attached as a reference for other FDA reviewers, but "red-lined" FDA comments have not been included in it.

RECOMMENDED REGULATORY ACTION:

**NDA, Efficacy/Label supplement :
Approve with labeling changes**

SIGNATURES:

Medical Reviewer: Joanna K. Zawadzki, M.D.

Date: January 12, 2007

Division Director: Mary Parks, M.D.

Date: _____

Review Summary

The sponsor has submitted reports for two bioequivalence studies and a food effect study in support of the proposed fixed-dose combination tablet **ACTOPLUS MET™ XR** (pioglitazone plus extended release metformin):

- Open-label, randomized, crossover study to assess the bioequivalence of the fixed-dose pioglitazone 15 mg/metformin extended release 1000 mg tablet to that of individual pioglitazone 15 mg and metformin XR 1000 mg tablets.
- Open-label, randomized, crossover study to assess the bioequivalence of the fixed-dose pioglitazone 30 mg/metformin extended release 1000 mg combination tablet to that of individual pioglitazone 15 mg and metformin XR 1000 mg tablets.
- Open-label, randomized, crossover, food-effect study to determine the effect of food on the exposure of pioglitazone and metformin after administration of the fixed-dose pioglitazone 15 mg/metformin extended release 1000 mg combination tablet.

As a 505(b)(2) application, the review and approval of this application rely on information from studies not conducted by or for the sponsor (TGRD) and a right of reference has not been obtained. A pediatric waiver is requested.

The primary review for this application was completed by clinical pharmacology (Jaya Vaidyanathan, Ph.D.), who recommended approval of **ACTOPLUS MET™ XR** (pioglitazone plus extended release metformin). I concur with her recommendation.

The proposed indication for **ACTOPLUS MET XR** is the same as for ACTOPLUS MET (NDA 21-842 approved 8/29/05, which comprises pioglitazone/metformin 15mg/500mg and 15mg/850mg fixed-dose tablets): “adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.” Even though **ACTOPLUS MET™ XR** (pioglitazone plus extended release metformin) may replace treatment with ACTOPLUS MET, there is no direct comparison between these two drugs, and the doses of metformin differ. The standard comparison that is recommended to show bioequivalence is a comparison of the combination drug to the constituent drugs, as was done in this application.

Extended-release metformin (**FORTAMET®**, Andrx Labs, LLC) was approved as NDA-21-574 (April 27, 2004). Metformin extended release given once daily was compared to the marketed reference immediate release metformin drug, Glucophage (Bristol Myers Squib) given twice daily. Dose equivalency for doses lower than 1000 mg was not established, and only the 1000 mg tablet was approved. The clinical reviewer of that application (R. Misbin, M.D.) hypothesized that the increasing dose was associated with decreasing absorption, and that this phenomenon accounted for some of the difference seen between the two products. For this reason, Glucophage 1000 mg given twice daily appeared to be more effective than Fortamet 2000 mg given once daily. However, this

difference was small, and it was offset by the convenience and theoretical likelihood of greater compliance with once-daily rather than twice-daily dosing.

Labeling Comments

The sponsor has 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. The sponsor proposes that either dose of ACTOPLUS MET XR may be used as the initial dose and a titrated maximal dose is not stated in the prescribing information. The maximum daily dose should be stated.

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

The **CLINICAL PHARMACOLOGY** section states: *Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR γ)* (lines 98-99 of submitted PI). This information is incorrect and should be modified to indicate that pioglitazone is an agonist for both peroxisome proliferator-activated receptors-gamma and alpha (PPAR γ a). In the **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility** section, the prescribing information states

(b) (4)

. This wording is misleading and should also be corrected.

Recommendation

The labeling comments should be forwarded to the sponsor.

Appendix: Sponsor's submitted Prescribing Information

cc: M. Parks, M.D., R. Misbin, M.D., J. Vaidyanathan, Ph.D., J. Weber, E. Galliers, L. AlJuburi

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as draft labeling (b)(4).

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/s/

Joanna Zawadzki
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MEDICAL OFFICER

Mary Parks
1/14/2007 12:42:36 PM
MEDICAL OFFICER
see additional comments on this application in division director
memo