

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-024

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 22-024

Name of Drug: Actoplus Met XR (pioglitazone HCl + metformin HCl) Fixed-Dose Combination Tablets

Sponsor: Takeda Global Research & Development Center, Inc.

Submission Date (AZ): April 30, 2008

Material Reviewed:

<u>Submission Date</u>	<u>Receipt Date</u>	<u>Document Type</u>
December 10, 2008	December 11, 2008	Revised carton & container labels
March 25, 2009	March 26, 2009	Revised PI and Med Guide

Background and Summary

This new drug application provides for the use of ACTOPLUS MET XR 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.

An approvable letter was issued to this NDA file on February 2, 2007. Takeda responded with a major amendment (AZ) on April 30, 2008.

Final carton and container labels were submitted on December 10, 2008. These were found acceptable as noted in the review from DMEPA dated December 17, 2008.

The agreed-upon FDA/Takeda PI and Med Guide labels were submitted on March 25, 2009.

Review:

Package Insert: Acceptable; FDA comments sent to Takeda on 3/18/09; compared to revised submission from company dated 3/25/09. Takeda accepted and inserted changes as requested. No discrepancies noted.

Med Guide Acceptable; FDA comments sent on 3/18/09, compared to revised submission from Takeda dated 3/25/09. No discrepancies noted from FDA requested version. Takeda accepted and inserted changes as we requested.

Carton & Container Labels: Acceptable as per DMEPA review dated 12/17/08.

Tradenname: Acceptable as per DMEPA review dated 4/30/09.

Conclusion:

An approval letter issued for NDA 22-024. SPL was submitted on April 1, 2009. This will be forwarded to NLM.

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this page is the manifestation of the electronic signature.**

/s/

Jena Weber
5/15/2009 07:23:10 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-024 Supplement # Efficacy Supplement Type SE-

Proprietary Name: ACTOPLUS MET XR
Established Name: pioglitazone + metformin extended-release (FDC)
Strengths: 15 mg/1000 mg; 30 mg/1000 mg.

Applicant: Takeda Global Research & Development Center, Inc.
Agent for Applicant: NA

Date of Application: April 30, 2008

Date of Receipt: May 1, 2008

Date clock started after UN:

Date of Filing Meeting: June 23, 2008

Filing Date: July 01, 2008

Action Goal Date (optional):

User Fee Goal Date: **November 1, 2008**

Indication requested: This new drug application provides for the use of ACTOPLUS MET XR 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.

Type of Original NDA: (b)(1) (b)(2) X
AND (if applicable)

Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: Standard
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES

- Does the submission contain an accurate comprehensive index? YES
If no, explain:

- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA NO
2. This application is an eNDA or combined paper + eNDA YES
This application is: Combined paper + eNDA
This application is in: Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? ALL

3. This application is an eCTD NDA. NO
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES
- Is this submission a partial or complete response to a pediatric Written Request? NO

If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES
(DO notified).
- PDUFA and Action Goal dates correct in tracking system? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 68,462
- Are the trade, established/proper, and applicant names correct in COMIS? YES
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 11/10/05
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? YES
- Risk Management Plan consulted to OSE/IO? NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? N/A
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment?
If EA submitted, consulted to EA officer, OPS?
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/7/08

NDA #: 22-024

DRUG NAMES: ActoPlus Met XR

APPLICANT: Takeda

BACKGROUND: Actoplus Met XR is indicated as an 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. This NDA consists of 2 BE studies and 1 food-effect study. Takeda is the holder of the approved drug Actos (pioglitazone); Andrx is the holder of Fortamet (metformin extended-release)

ATTENDEES: Zawadzki, Parks, Vaidyanathan, Campbell, Jahng Lee, Weber

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization

Reviewer

Medical:	Joffe/Zawadzki/Mahoney
Secondary Medical:	
Statistical:	NN
Pharmacology:	NN
Statistical Pharmacology:	NN
Chemistry:	Al-Hakim/Frasier/Niu
Environmental Assessment (if needed):	Niu
Biopharmaceutical:	Choe/Vaidyanathan
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	
OPS:	
Regulatory Project Management:	Weber
Other Consults:	DRISK/DDMAC/DMEPA/DSRCS

Per reviewers, are all parts in English or English translation? YES

If no, explain:

CLINICAL

FILE

- Clinical site audit(s) needed? NO
- If no, explain:
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 21-574 (Fortamet); NDA 21-073 (Actos).

3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”). **This application provides for a fixed-dose combination product.**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under NO

21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
 - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s): **See below**

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

Certification under 21 CFR 314.50(i)(1)(i)(A)(4) pertaining to the FORTAMET (metformin HCl extended-release) component:

Paragraph IV Certification:

Takeda Global Research & Development Center, Inc. (TGRD) certify that to the best of our knowledge and belief that U.S. Patent No. 6,099,859; U.S. Patent No. 6,495,162; U.S. Patent No. 6,790,459; U.S. Patent No. 6,866,866 will not be infringed by the manufacture, use or sale of ACTOPLUS MET XR (pioglitazone HCl and metformin hydrochloride extended-release) tablets for which this application is submitted.

TGRD will comply with the requirements under 314.52(a), by providing a notice to each owner of the patent or their respective representatives and to the holder of the approved application for the drug product which is claimed by the patent and with the requirements under 21 CFR 314.52(c).

Please note, TGRD has been granted a licensing agreement with Andrx Pharmaceuticals, Inc. and subject to the FDA's filing of the application TGRD will provide notice pursuant to 314.52(a).

On behalf of Andrx Labs, LLC. Andrx has a 100% ownership in the following US patents, which are listed in the FDA publication, Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book) for NDA 21-574 for FORTAMET (metformin HCL extended-release) tablets 500 mg and 1000 mg:

Patent No. Patent Expiration
6099859 March 20, 2018
6495162 March 20, 2018
6790459 March 17, 2021
6866866 March 17, 2021

The immediate approval of NDA 22-024 for ACTOPLUS MET TM XR by the US Food and Drug Administration will not infringe on any of the above listed patents due to inter-company license agreements between Andrx and Takeda Pharmaceutical Corporation, Ltd. and its wholly owned subsidiaries, Takeda Pharmaceuticals North America, Inc. (TPNA) and Takeda Global Research & Development Center, Inc (TGRD).

Andrx has no objection to the immediate approval of NBA 22-024 for ACTOPLUS MET XR by the US Food and Drug Administration prior to the expiration of the exclusivity period for NDA 21-574.

The following patents that appear in the publication Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book) will not be infringed by NDA 22-024 for ACTOPLUS MET XR:

Patent No. Patent Expiration
4,687,777 Jan 17, 2011
5,965,584 Jun 19, 2016
6,150,383 Jun 19, 2016
6,150,384 Jun 19, 2016
6,166,042 Jun 19, 2016
6,166,043 Jun 19, 2016
6,172,090 Jun 19, 2016
6,211,205 Jun 19, 2016
6,271,243 Jun 19, 2016
6,303,640 Aug 09, 2016
6,329,404 Jun 19, 2016

No claims of the listed patents will be infringed because Takeda Pharmaceutical Company Limited (TPC), the parent company of Takeda Global Research & Development Center, Inc. (TGRD) and Takeda Pharmaceuticals North America, Inc. (TPNA) has licensed these patents to TGRD and TPNA as explained in the attached letter from TPC

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s): **See above.**
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES

*If “Yes,” what is the listed drug product(s) Fortamet & Actos and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug: **All from original NDA’s.***

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

YES

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

NO

If “Yes,” please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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this page is the manifestation of the electronic signature.**

/s/

Jena Weber
3/30/2009 01:31:58 PM
CSO



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 17, 2008

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Jinhee J. Lee, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Actoplus Met XR (Pioglitazone HCl and Metformin HCl)
Extended-release Tablets
15 mg/1000 mg, 30 mg/1000 mg

Application Type/Number: NDA 22-024

Applicant: Takeda Global Research & Development Center, Inc.

OSE RCM #: 2008-1873

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Actoplus Met XR (OSE RCM #2008-493) on June 19, 2008 in which we made various recommendations regarding the proposed container labels and carton labeling. Subsequently, the Applicant submitted their revisions addressing DMEPA's requested changes.

2 MATERIAL REVIEWED

DMEPA reviewed our initial labeling review for Actoplus Met XR signed on June 19, 2008 in OSE RCM #2008-493 and we also reviewed the revised labels submitted by the Applicant dated December 10, 2008. See Appendices A through C for pictures of the labels and labeling.

- Commercial and Sample Container Labels: 15 mg/1000 mg, 30 mg/1000 mg
- Sample Blister: 15 mg/1000 mg, 30 mg/1000 mg (7 tablet package)
- Sample Display Tray: 15 mg/1000 mg, 30 mg/1000 mg (7 tablet package)

3 DISCUSSION

The Applicant has changed the container labels and carton labeling according to our recommendations and we have no further comments.

4 CONCLUSIONS AND RECOMMENDATIONS

The Applicant has satisfactorily revised the labels and labeling per our August 2008 request.

If you have any questions or need clarifications, please contact Mildred Wright, OSE Project Manager, at (301) 796-1027.

5 APPENDICES

Appendix A – Commercial and Sample Container Labels: 15 mg/1000 mg, 30 mg/1000 mg

(b) (4)



(b) (4)

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/s/

Jinhee Lee
12/17/2008 07:12:12 AM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
12/18/2008 05:35:53 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/18/2008 06:12:48 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 5, 2008

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Claudia Karwoski, Pharm D, Director (Acting)
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: Review of:

- Patient Labeling (Medication Guide)
- Proposed REMS

Drug Name(s) and Application Numbers:

- NDA 22-024 Actoplus Met XR
- NDA 21-842/S-009 Actoplus Met

Applicant/sponsor: Takeda Global Research & Development (TGRD)

OSE RCM #: 2008-1646

1 INTRODUCTION

This review is in response to a request by the Division of Metabolic and Endocrine Products (DMEP) to review the proposed Medication Guides and Risk Evaluation and Mitigation Strategies (REMS) for Actoplus Met and Actoplus Met XR.

FDA requested that Takeda Global Research & Development (TGRD) convert the existing patient package insert (PPI) to Medication Guides (MG) for all pioglitazone-containing products consistent with the approved MG for other thiazolidinedione class drugs and patient labeling met one of the three triggering criteria for a MG set forth in 21 CFR 208.20.

The Agency subsequently clarified that a new MG after March 25, 2008 automatically triggers a REMS according to the Food and Drug Administration Amendments Acts (FDAAA). In addition to the MG, the proposed REMS for both products includes a timetable for assessment of the REMS by months 18, 3 years, and 7 years after the REMS is initially approved.

2 MATERIAL REVIEWED

- NDA 22-024, Actoplus Met XR Proposed REMS submitted by the sponsor on October 7, 2008.
- NDA 21-842/S-009, Actoplus Met Proposed REMS submitted by the sponsor on October 21, 2008.
- DRAFT Actoplus Met and Actoplus Met XR Medication Guide (MG) submitted by the sponsor on October 7, 2007.
- DRAFT Actoplus Met and Actoplus Met XR Professional Information (PI) submitted by the sponsor on October 7, 2008.

3 BACKGROUND

Takeda Global Research & Development (TGRD) received approval for an original New Drug Application, NDA 21-842 on August 29, 2005 for Actoplus Met (pioglitazone hydrochloride and metformin hydrochloride). DSRCS reviewed patient labeling in the form of a PPI for Actoplus Met on April 26, 2005 and July 28, 2005. On August 6, 2008 DMEP and TGRD participated in a teleconference in which the Agency requested that the sponsor convert the existing PPI for Actoplus Met to a MG consistent with 21 CFR 208.20 and with the approved MG for other thiazolidinedione class drugs.

TGRD submitted a New Drug Application, NDA 22-024, on March 31, 2006, with the proposed name Actoplus Met XR (pioglitazone hydrochloride and metformin hydrochloride extended release tablets). TGRD submitted a PPI at that time updating the current PPI for Actoplus Met to include information for Actoplus Met XR. DSRCS reviewed the revised patient labeling on December 20, 2006.

DMEP took an Approvable Action for NDA 22-024 on February 2, 2007 citing certain deficiencies. TGRD submitted a Complete Response to the Approvable Action on April 30, 2008. The sponsor submitted labeling which combines the Actoplus Met and

Actoplus Met XR product label, and addresses comments from the DSRCs December 20, 2006 review of the PPI.

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 provide FDA with new authorities to require sponsors of approved drugs to develop and comply with Risk Evaluation and Mitigation Strategies (REMS) section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008. On September 30, 2008 DMEP and TGRD participated in a telephone conference in which the Agency requested that TGRD submit a REMS for Actoplus Met. The Agency clarified that a request to NDA sponsor for a MG after March 2008 automatically triggers a REMS according to the Food and Drug Administration Amendments Acts (FDAAA). The proposed REMS includes a timetable for assessment of the REMS by months 18, 3 years, and 7 years after the REMS is initially approved. On October 1, 2008 DMEP and TGRD participated in a telephone conference regarding Actoplus Met XR, in which the Agency requested that TGRD convert the existing PPI a Medication Guide (MG) consistent with 21 CFR 208.20, for pioglitazone containing products, and consistent with the approved MG for other thiazolidinedione class drugs. The MG is to be submitted as a proposed REMS with a timetable for assessment of the REMS by months 18, 3 years, and 7 years after the REMS is initially approved. TGRD submitted an Amendment to a Pending Application on October 7, 2008 including the requested MG for Actoplus Met XR.

The current REMS submission dated October 16, 2008 is in response to an October 15, 2008 telephone call between TGRD and DMEP. At that time a request was made to submit the proposed REMS document in accordance with the template previously provided by DMEP. TGRD submitted the draft MG on October 7, 2008; therefore, DMEP informed TGRD that it was unnecessary to resubmit the MG.

4 DISCUSSION

4.1 MEDICATION GUIDE

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 8.6, and a Flesch Reading Ease score of 58.3%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 8.0 and a Flesch Reading Ease score of 62%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information

- ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4.2 PROPOSED REMS

The proposed REMS states that a Medication Guide will be dispensed with each ACTOPLUS MET XR prescription. The Medication Guide will be included at the end of the prescribing information as a perforated attachment.

The Timetable for Assessments is as follows:

1st FDAAA assessment: 18 months from approval

2nd FDAAA assessment: 3 years from approval

3rd FDAAA assessment: 7 years from approval

Takeda will submit the assessments within 60 days of the close of the intervals.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that The Sponsor’s proposed REMS for Actoplus Met XR and Actoplus Met generally meets the statutory requirements outlined under 21CFR 208 and in accordance with 505-1(d). We have the following comments:

1. The sponsor’s proposed timetable for assessments (6 months, 18 months, 3 years and 7 years) is acceptable. The Sponsor should submit for review a plan to evaluate patients' understanding about the safe use of ActoPlus Met or ActoPlus Met XR at least two months before it is administered. The submission should include:
 - All methodology and instruments that will be used to evaluate patients' understanding about the safe use of ActoPlus Met (or ActoPlus Met XR). This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)

- The expected number of patients surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with their methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and the correlation to the messages in the Medication Guide.
2. The sponsor may choose to combine the ActoPlus Met and ActoPlus Met XR evaluations into one as the safety messages will be the same. The sponsor should make sure that both patients of ActoPlus Met and ActoPlus Met XR are represented in the sampling and responses.
 3. The sponsor must comply with all of the Medication Guide Regulations as specified in 21 CFR 208. In particular:
 - The carton and container labels must comply with 21 CFR208.24 (d). To our knowledge these labels have not yet been submitted to the Agency for review.
 - Actoplus Met is supplied in bottles of 60 and 180 tablets. Actoplus Met XR is supplied in bottles of 30, 60, and 90 tablets. Since Actoplus Met and Actoplus Met XR are not supplied in unit of use packaging, there is concern that the larger size bottles may be repackaged prior to dispensing and thus there would not be sufficient numbers of Medication Guides if bottles are repackaged and dispensed to multiple patients. Under 21 CFR 208.24 (b) (1) sufficient numbers of Medication Guides must be provided.

It is reasonable to expect that one Medication Guide will be provided for every one month supply of Actoplus Met or Actoplus Met XR per packaging configuration, for example 3-5 Medication Guides for a 90 Tablet bottle and 6-10 Medication Guides for a 180 Tablet bottle, to allow for repackaging and dispensing to multiple patients.

We have the following comments on the Medication Guide:

1. In the section “What are Actoplus Met and Actoplus Met XR” we made the first statement consistent with the *Indications and Usage* section of the proposed Actoplus Met and Actoplus Met XR PI. We note that the Avandia PI includes dosage and administration information for using Avandia alone or in combination with other Oral anti-diabetic agents. The Actoplus Met and Actoplus Met XR PI does not include such information under *Indications and Usage* or under *Dosage and Information*; therefore, it is not included in this MG.
2. In the section “Who should not take Actoplus Met and Actoplus Met XR?”:

- We moved the statement “Certain patients with heart failure should not start taking Actoplus Met or Actoplus Met XR. See “What is the most important information I should know about Actoplus Met and Actoplus Met XR?” to the beginning of the section. We deleted the word “certain” and added the word “many” at the beginning of the sentence to make the language consistent with the Avandia MG. We agree with the sponsor that the second sentence should refer patients to the section “What is the most important information I should know...”
 - The remaining language in this section differs from the Avandia MG due to differences in the labeled *Contraindications*.
3. In the section “What should I tell my doctor before taking Actoplus Met or Actoplus Met XR, we moved up the bullet “are older than 80 years old.”
 4. In the section “How should I take Actoplus Met or Actoplus Met XR:
 - We deleted the bullet stating that (b) (4) Unlike the Avandia PI, there is no information included in either the Indications and Usage Section or the Dosage and Administration section in this PI regarding use of (b) (4)
 - The sponsor includes a bullet stating “If your body is under stress, for example: due to fever, trauma (such as a car accident), or surgery, the dose of your diabetes medicines may need to be changed. Call your doctor right away.” We concur with including this bullet and added the word “infection” after the word “fever.” This information is in the currently approved Actoplus Met PPI. We recommend adding this information to the Avandia MG as well.
 5. We added the section “What should I avoid while taking Actoplus Met or Actoplus Met XR?” This section is in the currently approved PPI for Actoplus Met and should be included in the MG for these products since patients are at risk for getting lactic acidosis due to the metformin hydrochloride component of these products.
 6. In the section “What are the possible side effects of Actoplus Met and Actoplus Met XR:
 - To eliminate redundancy, we have deleted the first four bullets- (b) (4) This information is in the section “What is the most important information I should know about Actoplus Met and Actoplus Met XR?” We recommend revising the Avandia MG similarly so that patients do not wrongly interpret the information and assume that Avandia is safer than ACTOPLUS MET or ACTOPLUS MET XR.
 - In the bullet “low blood sugar (hypoglycemia), we added the statement “This can happen because you are taking two medicines together to treat your high blood sugar.” The *Information for Patients* section of the PI states that

“Combination antihyperglycemic therapy may cause hypoglycemia.” We added language to specifically address the statement.

- We revised the language in the bullet for macular edema to make it consistent with the language in the Avandia MG.
- The review division should consider whether myalgia, tooth disorder, diabetes mellitus aggravation, and pharyngitis should be added to the list of common side effects. They appear in the box below Table 6 in the PI and reflect “Other adverse events reported in at least 5% of patients in controlled clinical trials between placebo and pioglitazone monotherapy. If so, add to the MG using patient-friendly language.

Please let us know if you have any questions.

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this page is the manifestation of the electronic signature.**

/s/

Mary Dempsey
11/5/2008 05:39:56 PM
DRUG SAFETY OFFICE REVIEWER

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 9, 2008

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Patient Labeling and Education Team
Division of Risk Management (DRISK)

Subject: Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Actoplus Met XR (pioglitazone and metformin hydrochloride
extended-release) tablets

Application Type/Number: NDA 22-024

Applicant/sponsor: Takeda Global Research & Development Center, Inc.

OSE RCM #: 2008-749

1 INTRODUCTION

Takeda Global Research & Development, Inc. submitted new NDA22-024 on March 31, 2006 for an extended release tablet, with the proposed name ACTOPLUS MET XR (pioglitazone hydrochloride and metformin hydrochloride extended-release) tablets. DSRCS reviewed a proposed PPI which updated the approved PPI to include information about ACTOPLUS MET XR, on December 20, 2006.

The review division took an Approvable Action for NDA 22-024 on February 2, 2007. A copy of the DSRCS review of the PPI was included in the Approvable letter sent to the sponsor.

The sponsor submitted a complete response to the Approvable letter of February 2, 2007, on April 30, 2008. The sponsor's complete response includes both a revised PI and PPI. This review of the sponsor's revised PPI is written in response to a request from the review division for review by the Patient Labeling and Education Team.

2 MATERIAL REVIEWED

- ACTOPLUS MET and ACTOPLUS MET XR Professional Information (PI) submitted on April 30, 2008
- ACTOPLUS MET and ACTOPLUS MET XR Patient Package Insert (PPI) submitted on April 30, 2008

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The revised draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.0, and a Flesch Reading Ease score of 60.6. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review comments below, to the sponsor's complete response, we have

- simplified wording and clarified concepts where possible,
- made the PPI consistent with the Professional Information,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The Patient Labeling and Education Team has recently reviewed the proposed Medication Guides for Avandamet and Avandaryl. The Boxed Warning for Actoplus MET and Actoplus Met XR pertaining to related to congestive heart failure is the same as

the boxed warning for all of the Avandia containing products. For consistency across Thiazolidinedione products, we recommend using the same language in the PPI section “What is the most important information I should know about Actoplus and Actoplus Met?” as is used in the Medication Guides for the Avandia-containing products.

2. After the last bullet in the section, “Who should not take Actoplus Met and Actoplus Met XR?”, we recommend adding the following free-standing statement, which appears in the Medication Guides for Avandia-containing products.

“Many patients with heart failure should not start taking Actoplus Met or Actoplus Met XR. See “What should I tell my doctor before taking Actoplus Met or Actoplus Met XR.”

3. In the section, “What should I tell my doctor before taking Actoplus Met and Actoplus Met XR?” “Tell your doctor about all your medical conditions, especially if you:”

- Change the word “especially” to “including.”
- Modify the first bullet to state “have heart problems.” Delete the additional language. This information is too complex for patients.
- Under “Tell your doctor about all the medicines you take...,” modify the third sentence to be consistent with language we just recommended for Avandamet and Avandaryl:

“Your doctor may need to change your dose of Actoplus Met or Actoplus Met XR, or certain other medicines.”

4. We note that in the approved PPI for Actoplus Met as well as in the proposed PPI under the section “How should I take Actoplus Met and Actoplus Met XR?” there is language to address both the need to stop the product which addresses concern about lactic acidosis, and loss of control of blood sugar. We suggest using the language, as appropriate, in the Medication Guides for the Avandia-containing products to convey these important messages.

5. Under the section “What are the possible side effects of Actoplus Met and Actoplus Met XR?”

- Following the format we suggested for Avandamet and Avandaryl, add the following immediately after the header: See “What is the most important information I should know about Actoplus Met and Actoplus Met XR?”
- Following this on a new line, add the following: Actoplus Met and Actoplus Met XR can cause other serious side effects, including:”
- Delete the bullets for (b) (4)

The first bullet above refers the reader back to that section.

6. The instructions for storing Actoplus Met and Actoplus Met XR are the same. Use a bulleted format for the storage instructions as follows:

- Store ACTOPLUS MET and Actoplus Met XR at 59°F to 86°F (15°C to 30°C), in its original container.
- Keep the bottle tightly closed. Protect from moisture and humidity.

Keep ACTOPLUS MET and ACTOPLUS MET XR and all medicines out of the reach of children.

7. In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We suggest that the sponsor format the PPI for Actoplus Met and Actoplus Met XR using one of these three fonts.
8. We recommend adding the following as a free-standing statement at the end of the section called “What are the possible side effects of Actoplus Met and Actoplus Met XR?”:

“Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.”

This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Actoplus Met and Actoplus Met XR, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

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/s/

Sharon Mills
6/9/2008 01:11:31 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
6/9/2008 01:14:05 PM
DRUG SAFETY OFFICE REVIEWER



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: June 19, 2008

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention

From: Jinhee J. Lee, PharmD, Safety Evaluator
Division of Medication Error Prevention

Subject: Medication Error Labeling Review

Drug Name: Actoplus Met XR (Pioglitazone and Metformin HCl)
Extended-release Tablets
15 mg/1000 mg, 30 mg/1000 mg

Application Type/Number: NDA 22-024

Applicant: Takeda Global Research & Development Center, Inc.

OSE RCM #: 2008-493

CONTENTS

EXECUTIVE SUMMARY	2
1 BACKGROUND	2
1.1 Introduction	2
1.2 Product Information	2
2 METHODS AND MATERIALS	2
3 RESULTS	3
3.1 Response to Applicant’s Comments	4
4 DISCUSSION	5
5 CONCLUSIONS and RECOMMENDATIONS	7
5.1 Comments to the Division	7
5.2 Comments to the Applicant	7
6 APPENDICES	9

EXECUTIVE SUMMARY

The Division of Medication Error Prevention reviewed the applicant's responses to the recommendations made in an IR letter issued on January 8, 2007 about their submitted container labels and carton labeling. For the most part, we were in agreement with their responses, but noted additional improvements could be made to decrease the potential for selection errors and to increase readability of information presented on the labeling. For full recommendations, we refer you to section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This memorandum is in response to a May 6, 2008 request from the Division of Metabolism and Endocrinology Products for a review of the applicant's response to our labels and labeling comments. We note that the applicant stated in their letter to the Division that the container labels and carton labeling have been revised.

The Division of Medication Error Prevention originally reviewed the container labels and carton labeling and forwarded comments to DMEP in two reviews dated January 8, 2007 (OSE Review #06-0201) and May 10, 2007 (OSE 2007-609).

1.2 PRODUCT INFORMATION

Actoplus Met XR is an oral antihyperglycemic agent indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It is an extension of the Actoplus Met product line. Actoplus Met, approved on August 29, 2005, is an immediate-release combination tablet of pioglitazone and metformin HCl indicated for the treatment of patients with type 2 diabetes. Actoplus Met is available in 15 mg/500 mg and 15 mg/850 mg tablets. Actoplus Met may be dosed once or twice daily.

Actoplus Met XR is for use in patients who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone. Actoplus Met XR will be available as a combination tablet containing an immediate-release active ingredient (pioglitazone HCl) and an extended-release active ingredient (metformin HCl). Actoplus Met XR will be available in two different strengths: 15 mg/1000 mg and 30 mg/1000 mg. This product is indicated as a once-daily product, but the dosage should be individualized based on a patient's current treatment with each drug component or based on a patient's treatment requirements for effectiveness and tolerability. The commercial product will be supplied in 30, 60, and 90 count bottles. Physician samples will be supplied in 7 count blister packaging.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error and Prevention medication error staff conducting a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or

patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, the Division of Medication Error Prevention staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on April 30, 2008 the following labels and insert labeling for the (see Appendices A, B, C for images)

- Retail Container: 15 mg/1000 mg, 30 mg/1000 mg
- Sample Blister: 15 mg/1000 mg, 30 mg/1000 mg (7 tablet packages)
- Sample Display Tray: 15 mg/1000 mg, 30 mg/1000 mg (7 tablet package)
- Package Insert Labeling (no image)

The Division of Medication Error Prevention compared the revised labels to both the current and previously proposed labels to identify any outstanding areas of concern from a medication errors perspective. We note that there were some recommendations that were overlooked in the previous review that we would like to bring to attention in this one. These recommendations represent new areas of concern from a medication errors perspective and are noted below. In addition, we will comment on the applicant's responses, if any, below.

3 RESULTS

The Division of Medication Error Prevention notes that the revised labels and labeling are generally consistent with the requests and comments forwarded to the applicant on May 10, 2007. However, we have identified some new and outstanding areas of concern.

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.1 RESPONSE TO APPLICANT'S COMMENTS

3.1.1 General Comments

The Division of Medication Error Prevention acknowledges that the applicant has revised the DESCRIPTION section of the package insert by (b) (4) the (b) (4) from the established name and expressing the tablet strength as the pioglitazone base. We also recognize that the applicant has revised the carton and container labels to remove the (b) (4) following the established name, pioglitazone, to accurately reflect the tablet strength as the base and (b) (4). Furthermore, we acknowledge that the applicant has revised the presentation of the established name to improve the spacing to appear less crowded. However, we note that the most recently approved version of the prescribing information for Actos retains the "pioglitazone hydrochloride" nomenclature in the established name.

We acknowledge that the applicant has revised the font of the word "plus" on all labels and labeling to be consistent with the remainder of the proprietary name.

3.1.2 Container Labels

We acknowledge that the applicant has revised all container labels and carton labeling as advised by the Division of Medication Error Prevention.

We acknowledge that the product name and strength have been made more prominent by increasing the font size and separating the strength from the established name on the appended draft packaging. We note that this presentation is in accordance with our recommendations made on May 10, 2007.

3.1.3 Sample Blister Labels

We acknowledge that the applicant has removed the "+" sign, and has replaced the sign with the word "and" in the established name throughout all container labels and carton labeling.

We acknowledge that the applicant has revised the blister packaging to a different layout configuration and also is utilizing different colors for each product. However, we note that the applicant may be utilizing a purple font color for both the Actoplus Met and Actoplus Met XR products.

We acknowledge that the applicant has inserted the product strength directly below the names in the purple panel, and has included the strength in all instances where the product name exists. We also acknowledge that the applicant has included appropriate spacing between the last digit of the strength and the unit.

We acknowledge that the applicant has removed the overlapping color on the two product strengths of Actoplus Met XR and that the bright pink color is now applied only to the 30 mg/1000 mg strength.

We acknowledge that the applicant has taken steps to distinguish the blister packaging for Actoplus Met from the Actoplus Met XR product.

We note that the applicant has stated that the colors utilized for Actoplus Met are different than what is used for Actoplus Met XR. However, we note that Actoplus Met 15 mg/850 mg labels appear similar to the Actoplus Met XR 15 mg/1000 mg strength container label. We also note that the sample labels (i.e. display tray, carton, and blister) appear in a purple color.

We acknowledge the applicant's comment to clarify our response about the presentation of the lot numbers and expiration dating on the blister packaging. We acknowledge that the applicant

proposes that the panel containing the tablets will include the proprietary and established names, strength, lot numbers, and expiration dating. We would also like to note that the applicant has not responded to our comment about scissors commonly being used to cut out tablets from blister cards so that they can be easily carried in a patient's purse, wallet, or clothing pocket.

3.1.4 Sample Display Tray Labeling

We acknowledge that the applicant has applied revisions we proposed to all sample display tray labeling for this product.

We note that the applicant has not included the statement, "Do not chew, crush or cut tablet" to the carton labeling.

3.1.5 Package Insert Labeling

We note that the applicant has included the abbreviation, "q.d.", to describe "once-daily".

4 DISCUSSION

The Division of Medication Error Prevention acknowledges that the applicant has revised the DESCRIPTION section of the package insert by (b) (4) the (b) (4) from the established name and expressing the tablet strength as the pioglitazone base. We also recognize that the applicant has revised the carton labeling and container labels to remove the (b) (4) following the established name, pioglitazone, to accurately reflect the tablet strength as the base and (b) (4). Furthermore, we acknowledge that the applicant has revised the presentation of the established name to improve the spacing to appear less crowded. However, we note that the most recently approved version of the prescribing information for Actos retains the "pioglitazone hydrochloride" nomenclature in the established name.

The applicant (b) (4) the (b) (4) from the established name and expressed the tablet strength as the pioglitazone base to comply with the standard accepted by CDER. However, we note that the applicant's product, Actos, which also contains the active ingredient "pioglitazone hydrochloride", does not comply with this same standard. For consistency, we believe that the presentation of this information should also be revised and expressed in accordance with CDER's standard. The standard accepted by CDER is to (b) (4) the (b) (4) from the established name and express the strength without the use of any asterisk.

The applicant submitted labels using color schemes that bear a remarkable similarity to the color schemes utilized for their already existing product line, Actoplus Met. In particular, we are concerned with the color scheme for the Actoplus Met 15 mg/850 mg container label which overlaps with the Actoplus Met XR 15 mg/1000 mg container label. Additionally, we are concerned about the overlap of purple color schemes for the professional sample blister cards (see Table 1 on page 6).

(b) (4)



While we recognize that the Actoplus Met 15 mg/850 mg strength is not an exact color match to the Actoplus Met XR 15 mg/1000 mg color, we remain concerned because the color is in that “purple” color family. The Actoplus Met and Actoplus Met XR product lines by themselves would not appear to be problematic, however, the fact that Actoplus Met and Actoplus Met XR will most likely sit adjacent to each other on the pharmacy shelf, in conjunction with the overlapping color scheme, strengths (i.e. 15 mg), and root names, increases the potential for selection errors. The color that captures the reader’s attention is the bold color scheme that serves as a background for the proprietary and established names and tablet strength numbers. Additionally, we have concerns that confirmation bias may also contribute to the potential that the healthcare provider will select the wrong product.

Because the Actoplus Met XR is a combination tablet containing an immediate-release and an extended-release active ingredient, it is imperative that the tablet is not chewed, crushed, or cut, to maintain the integrity of the tablet’s components and performance. In a previous review, we had made the recommendation to include the statement, “Do not chew, crush or cut tablets” to the container labels and carton labeling. The applicant added this statement to the container labeling, but has neglected to include it on the carton labeling. In order to clearly convey this information and prevent chewing, crushing, or cutting of the tablet, we believe it is imperative to include this information on the carton labeling (i.e. tray).

The abbreviation “q.d.” is used to describe “once-daily” in the package insert labeling. Our post-marketing surveillance demonstrates that the use of abbreviations such as “QD”, have resulted in confusion with other abbreviations such as “QID” and should be avoided if possible. On June 14, 2006, the FDA and the Institute for Safe Medication Practices (ISMP) launched a nationwide health professional education campaign³ aimed at reducing the number of common but preventable sources of medication mix-ups and mistakes caused by the use of trailing zeros and unclear medical abbreviations. Therefore, the “q.d.” abbreviation should be removed in keeping with this campaign.

Additionally, while the applicant has proposed to include the proprietary and established names, strength, lot numbers, and expiration dating on the blister label panel, they have not responded to our comment about scissors commonly being used to cut out tablets from the blister cards. We remain concerned that the blister label may be separated in this manner without any identifying information about the product and believe that each individual blister should contain the aforementioned information to avoid confusion.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the colors used for two of the strengths introduce new areas of vulnerability to confusion that could lead to medication errors. This confusion stems from an overlapping color scheme with the existing Actoplus Met product line. The Division of Medication Error Prevention believes this risk can be mitigated by differentiating the proposed labels and labeling from the Actoplus Met product line and by revising the labels and labeling as suggested.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant. Please copy the Division of Medication Errors Prevention on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, OSE Project Manager, at 301-796-0723.

5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention identified the following areas of need improvement.

1. Ensure that all products containing pioglitazone hydrochloride are presented so that the (b) (4) is (b) (4) from the established name and the strength is expressed without the use of any asterisk.

³ <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01390.html>

2. Ensure that the Actoplus Met XR 15 mg/1000 mg color scheme does not overlap with the Actoplus Met 15 mg/850 mg or 15 mg/500 mg color schemes. Similarly, ensure that the colors utilized for the Actoplus Met and Actoplus Met XR blister labels do not overlap with each other.
3. Revise the sample display tray to include the following statement: “Do not chew, crush or cut tablets”.
4. Remove the “q.d.” abbreviation from the insert labeling.

3 pp withheld immediately after this page as draft
labeling (b)(4)

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

/s/

Jinhee Jahng
6/19/2008 02:50:23 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
6/19/2008 04:08:16 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/20/2008 02:54:09 PM
DRUG SAFETY OFFICE REVIEWER



NDA 22-024

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

Dear Ms. Cosner:

Please refer to your March 31, 2006, new drug application (NDA) submitted under section 505(b) 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.

The Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety (ODS) has completed their review of your submission dated January 29, 2007. In the review of the labels and labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error. Please address the following comments in writing to your NDA file.

A. GENERAL COMMENTS

1. FDA letter dated January 8, 2007: According to the **DESCRIPTION** section of the package insert labeling, the strength of pioglitazone is based on the active moiety and not the hydrochloride salt. However, the manner in which this information is presented on the labels and labeling does not express the same information and instead, it appears the milligram amount pertains to the amount of salt and not the base. We recommend revising this section so that it states the strength of each tablet accurately. For guidance on this presentation, contact Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee.

Takeda Response dated January 29, 2007:

TGRD concurs that the **DESCRIPTION** section of the package insert states that pioglitazone is based on the active moiety and not the salt. The package insert (line 54) states, "ACTOPLUS MET XR is available as a tablet for once-a-day oral administration containing xx mg pioglitazone hydrochloride (as the base) with xxxx mg metformin hydrochloride (xx mg/ xxxx mg)..." The labels and labeling are all also presented in a similar manner as "pioglitazone HCl xx mg* and metformin HCl extended-release xxxx mg Tablets".

The asterisk is defined on the label as “Each film-coated tablet contains xx mg of pioglitazone base and xxxx mg of metformin HCl.” TGRD has represented pioglitazone based on the active moiety and not the salt.

For your reference, the ACTOPLUS MET product approved on August 29, 2005, and submitted as final printed labeling on October 24, 2005, has presented the concentration of active moiety as presented above. This also applies to the package insert and all labeling recently approved for the fixed-dose combination product of pioglitazone and glimepiride (DUETACT). In addition, the product labeling for ACTOS, contains a statement that the strength is based on the active moiety (base) of pioglitazone on all pioglitazone products and is consistent with the description in each package insert.

DMETS response: We recognize this presentation was approved with Actoplus Met on August 29, 2005. However, since that approval there has been much discussion in the Agency about the standard presentation of this information. The standard accepted by CDER is to remove the salt from the established name and express the strength without the use of any asterisk. We refer you to Rick Lostritto for future guidance in this CDER LNC decision. Additionally, in the current presentation, the established name appears crowded on the label.

2. FDA letter dated January 8, 2007: The word “plus” in Actoplus Met XR is italicized. Revise the font of “Plus” so it is consistent with the remainder of the proprietary name in accordance with 21 CFR 201.10(g)(2).

Takeda Response dated January 29, 2007: Takeda proposes to keep the trade name “Actoplus Met XR” as submitted with the word “plus” italicized on all product labeling. This is consistent with Takeda’s immediate-release product, ACTOPLUS MET, in which the carton and container labels were agreed to during a teleconference with the Agency on August 25, 2005, and TGRD subsequently submitted Final Printed Labeling for the ACTOPLUS MET NDA 21-842 on October 24, 2005. Takeda believes that it is important to keep the same typographical presentation within the family of products since they contain the same active ingredients.

DMETS Response: DMETS has recommended revising the font of “plus” so that it was consistent with the remainder of the proprietary name in accordance with 21 CFR 201.10(g)(2). Similarly, with “Duetact,” we recommended using one uniform font style. We acknowledge that this italicization is consistent with the already marketed product Actoplus Met, however, DMETS recommends revising the font so that prominence is not given to the plus sign but to the entire product name solely.

3. FDA letter dated January 8, 2007: We note that you propose to market 30, 60, and 90 count tablet bottles. We consider these as unit-of-use bottles. Please ensure that the containers have a Child Resistant Closure (CRC) cap in order to be compliant with the Poison Prevention Act.

Takeda Response dated January 29, 2007: TGRD will ensure that the [REDACTED] (b) (4)

DMETS acknowledges your comments and has no further recommendations.

4. FDA letter dated January 8, 2007: The labeling indicates that Actoplus Met XR must be swallowed and not chewed, cut, or crushed. Post-marketing evidence has shown that labels and labeling that do not clearly convey this information have been inadvertently chewed, crushed, or cut. In order to minimize this administration error, DMETS recommends repeating this statement on the container labels and carton labeling, especially since the 30, 60, and 90 count bottles can be dispensed as unit-of-use.

Takeda Response dated January 29, 2007: TGRD agrees with DMETS request and has added the statement, “Do not chew, crush or cut tablets” to the container labeling for the 30, 60, 90 count bottles [REDACTED] (b) (4).

DMETS acknowledges your comments and has no further comments.

B. CONTAINER LABELING

1. Takeda Response dated January 29, 2007: See responses to A1 and A2 above which apply to all container and carton labeling.

DMETS Response: See comments made in A1 and A2.

2. FDA letter dated January 8, 2007: Although the proprietary and established names and strength are highlighted, they do not appear to be the most prominent information on the labels. This important information blends in with the remaining text on the label because everything appears to be of similar font size. Revise the labels so that the proprietary and established names, as well as the strength, are the most prominent information on the label by increasing the font, bolding or some other means.

Takeda Response dated January 29, 2007: TGRD has revised the container labeling by decreasing the font of the remaining text on the container labeling to improve the prominence of the product name and strength. Also, the tablet quantity was unbolded and moved up one line, along with the NDC number, allowing for more space between the color block containing the product name and the tablet count text. In addition, by decreasing the size of the text below the box, an extra line space was created in between the bottom of the color block and the remaining text below. Upon making these revisions, TGRD believes that the proprietary and established names as well as the strength are not the most prominent information on the labels. Please refer to the revised sample labels contained in this submission.

DMETS Response: Although the font of the remaining text on the container labeling has been decreased, the product name and strength continues to lack prominence. Additionally, the pioglitazone strength, 15 mg, is difficult to decipher as it is embedded within the text.

The current presentation deviates from how most labels and labeling present their proprietary and established names and strength. Typically, the names and strength as presented as:

**Actoplus Met XR
(pioglitazone and metformin HCl) extended-release tablets
15 mg/1000 mg**

We suggest that you present the name and strength as demonstrated above to improve readability and to increase prominence.

3. FDA letter dated January 8, 2007: The net quantity statement appears more prominent than the strength. Revise the labels so that the strength is more prominent.

Takeda Response dated January 29, 2007: TGRD has revised the label by decreasing the font and unbolding the net quantity statement. There is also additional white space above and below the color block allowing for a greater separation of the proprietary and established name as well as strength and the rest of the text on the labeling. Thus, the strength of the product now appears more prominent than the net quantity of the container.

DMETS acknowledges that you have revised the net quantity statement by decreasing the font and unbolding it. However, we disagree with your assessment of the prominence of the product strength. See comment B2 above.

(b) (4)

(b) (4)

With regards to the comment that you would like to present Actoplus Met and Actoplus Met XR similarly “since they both contain the same active ingredients,” we are concerned that having Actoplus Met XR labels and labeling that are too similarly presented to Actoplus Met, will encourage confusion and increase the occurrence of medication error.

In particular, because both Actoplus Met and Actoplus Met XR have an overlapping pioglitazone strength (15 mg) which appears before the metformin strength, health care providers might mistakenly select the wrong product. This possibility exists even more so because products are often placed on the pharmacy shelf in alphabetical order. Moreover, post-marketing evidence demonstrates that errors have occurred within manufacturer product lines that overlap in ingredient and strength. Thus, we reiterate the importance of differentiating the two products, Actoplus Met and Actoplus Met XR, from each other, even if they are in the “family of ACTOS products.” Interchanging the products with each other inadvertently may adversely affect the recipient of the patient and should be avoided if possible. Therefore, please revise all labels and labeling by removing the plus sign (+) and replacing with the word “and.”

(b) (4)

Takeda Response dated January 29, 2007: TGRD will ensure that the professional sample for ACTOPLUS MET XR will include a child resistant container, as we have the ACTOS, ACTOPLUS MET and DUETACT which are all available as (b) (4).

DMETS has no further comments.

4. FDA letter dated January 8, 2007: On the front inside panel, the product strength is present without the proprietary or established names. Revise labels so that the proprietary and established names appear and are positioned so that they are above the product strength. Also, it is difficult to read the grey/lavender font color against the pink background. Revise the colors to improve readability.

Takeda Response dated January 29, 2007: TGRD has removed the product strength from the inside panel when it appears without the proprietary and established names. Thus, there is no longer grey/lavender font color against the pink background. TGRD has revised all font color to black that is against the pink background to improve readability. TGRD has also revised the labeling so that each time the strength is presented, both the established and proprietary names are present and positioned above the product strength. The bottom left side of the inside panel appropriately contains the proprietary and established names along with the product strength. Please refer to the revised sample labels contained in this submission.

DMETS acknowledges your revisions. We also recommend that you insert the product strength immediately below the proprietary and established names present in the purple panel on top. Please include a space between the last digit and the unit, mg, to read XX mg/XXXX mg. For further reference, see comment B2.

(b) (4)



5. **FDA letter dated January 8, 2007:** You use the same two colors on the package of both strengths (e.g., purple and bright pink). When compared side-by-side, the overlap in color is especially noticeable since these colors are positioned in an identical format. Additionally, the only variance in appearance lies in the use of lavender or white as the third block color (see picture on page 8). Having the same color schemes makes it difficult to differentiate between the strengths. To minimize confusion and the occurrence of selection errors, revise the colors so that they are distinct from each other.

Takeda Response dated January 29, 2007: TGRD has revised the color scheme on all sample blister labeling to more clearly differentiate the two tablet strengths. TGRD has removed the dark purple block color from both the front and back of both the inside and outside panel for the 30 mg/1000 mg strength package and replaced it with the color white. The 15 mg/1000 mg product strength is now identified with a lavender background with a dark purple banner on top.

The 30 mg/1000 mg product strength is now identified with a white color background for the product name and strength. Thus the only overlapping color for both strengths is the bright pink sections which will clearly identify that these two packages are of the same product family, while still differentiating the two product strengths. Please refer to the revised sample labels contained in this submission.

DMETS Response: While we acknowledge that you have taken steps to differentiate the product strengths from each other, we remain concerned that both strengths resemble each other because they utilize the same bright pink color in their respective packaging (see below). Having *any* color overlap is concerning and may inevitably lead to confusion. The bright pink color is very prominent and we recommend using it for only one of the strengths.

(b) (4)



We also note that the format of these (b) (4) are similar if not identical to the Actoplus Met labels and we are concerned that this overlap may lead to selection errors resulting from confirmation bias. We are especially concerned with the potential for confusion between the Actoplus Met products and Actoplus Met XR 15 mg/1000 mg strength. Postmarketing evidence has demonstrated confusion and subsequent error has occurred between products that share a similar name and have an overlapping strength. Additionally, there are numerous cases in which similar packaging has contributed to selection errors, even if the names do not overlap. For these reasons, we recommend that the colors and the layout of the (b) (4) be revised as well.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted] (b) (4)

DMETS acknowledges your revisions and have no further comments regarding the changes you have made. In summary, DMETS recommends implementation of the label and labeling revisions as outlined above.

If you have any questions, please call Ms. Jena Weber 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
5/10/2007 08:54:29 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 27, 2006

TO: David Orloff, M.D.
Director
Division of Metabolism and Endocrine Drug
Products

FROM: Jagan Mohan R. Parepally, Ph.D.
Staff Fellow
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-024,
Actoplus Met XR (Pioglitazone HCl and Metformin
HCl extended release) Tablets, Sponsored by
Takeda Global Research & Development Center, Inc.

At the request of the Division of Metabolism and Endocrine Drug Products (DMEDP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of following bioequivalence studies:

Study 01-04-TL-OPIXT-002: An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release(XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets.

Study 01-04-TL-OPIXT-003: An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release(XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets.

The clinical portion of studies 01-04-TL-OPIXT-002 and 01-04-TL-OPIXT-003 were conducted at (b) (4)

Analytical portions of both studies were conducted at (b) (4). Following the inspection of (b) (4)

(December 6-13, 2006) and (b) (4) (December 11-15, 2006), Form FDA-483 was issued (Attachment 1). No objectionable findings were noted and Form FDA-483 was not issued at (b) (4). The objectionable items and our evaluation are provided below:

(b) (4)

- 1. An investigation was not conducted in accordance with the investigational plan.**
- 2. Failure to prepare or maintain accurate case histories with respect to observations and pertinent to the investigation and informed consent.**

Contrary to the protocol, informed consent and clinical laboratory tests were not obtained at screening for Subject# 1001. Instead, consent and clinical laboratory tests were obtained prior to dosing of the subject. The clinical laboratory results were normal and there were no adverse events reported for the subject during the study. The above protocol deviation does not compromise the safety of the subject. The firm should assure that they follow the protocol in future studies.

Although, informed consent and laboratory tests were not obtained at screening, the case report form (CRF) erroneously states the consent and laboratory tests were done at screening for subject 1001. The firm should assure that CRFs accurately reflect source data for future studies.

(b) (4)

- 1. Approximately 90 study samples were re-assayed for Pioglitazone or Metformin due to pharmacokinetic reasons. No objective criteria were established a priori to justify selection of these study samples.**

The finding is unlikely to affect study outcome as less than 1% of the study samples were re-assayed for pharmacokinetic reasons and approximately 88% of the re-assayed samples were within 10% of the original concentrations. Nonetheless, the firm should have

Page 3 of 3 - NDA 22-024, ACTOPLUS MET™ XR tablets, 15 mg/1000 mg, 30 mg/1000 mg

established procedure for selecting pharmacokinetic repeats in future studies.

Conclusion:

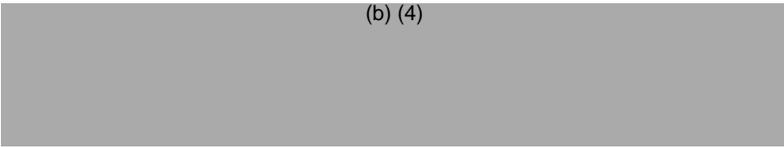
DSI recommends that the data obtained from the studies 01-04-TL-OPIXT-002 and 01-04-TL-OPIXT-003 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Jagan Mohan R. Parepally, Ph.D.

Final Classifications:

(b) (4)



cc:

HFD-45/RF

HFD-48/Parepally/Himaya/CF

DMEDP/Weber (WO22, RM3364, NDA 22-024)

HFR-CE850/Matson/Holaday

HFR-PA2565/Koller/Shire

HFR-CE750/Bellamy/Bizjak

Draft: JP 12/27/06

Edit: SS 12/27/06

DSI: (b) (4) O:\BE\EIRCOVER\22024 Actoplus Met XR.doc

FACTS: (b) (4)

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/s/

Jagan Parepally
12/27/2006 02:36:38 PM
PHARMACOLOGIST

Dr. Viswanathan signed the paper copy on 12/27/2006

C.T. Viswanathan
12/27/2006 02:48:15 PM
BIOPHARMACEUTICS