CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-842

CHEMISTRY REVIEW(S)

NDA 21-842

ActoPlus MET™

Takeda Global Research & Development Center, Inc.

William M. Adams
Division of Metabolism and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-842

2. REVIEW #1

3. REVIEW DATE: 06-Jul-2005

4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	27-Oct-2004
BC Amendment (response to 75-day comments)	18-Feb-2005
BC Amendment (updated stability & corrections)	01-Apr-2005
BC Amendment (response to 06/15/05 FAX	28-Jun-2005
BL Amendment	30-June-2005
BL Amendment	12-Jul-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Takeda Global Research & Development Center, Inc.
Address:	475 Half Day Road Lincolnshire, IL 60069
Representative:	Mary Jo Pritza, MPH, PharmD Manager, Regulatory Affairs
Telephone:	(847) 383-3730

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: ACTOPLUS MET™
   (b) Non-Proprietary Name (USAN): Pioglitazone HCl/Metformin HCl tablets
   (c) Code Name: AD-4833 MET tablets
   (d) Chemical Type/Submission Priority: 4S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: Anti-diabetic

11. DOSAGE FORM: Immediate release tablet

12. STRENGTH/POTENCY:
15mg PIO HCl/500mg MET HCl
15mg PIO HCl/850mg MET HCl

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___SPOTS product – Form Completed
XX Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pioglitazone HCl	
Chemical Name	(±)-5-[*p*-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione HCl
Chemical Formula	$C_{19}H_{20}N_2O_3S \cdot HCl$
Molecular Weight	392.90
Metformin HCl	
Chemical Name	*N,N*-Dimethylimidodicarbonimidic diamide HCl
Chemical Formula	$C_4H_{11}N_5 \cdot HCl$
Molecular Weight	165.62

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	III			3	Adequate	12/06/04	---
	III			3	Adequate	07/27/04	---
	III			3	Adequate	pending	---
	III			3	Adequate	07/31/01	---
	III			3	Adequate	04/05/02	---
	III			3	Adequate	01/07/04	---
	II			3	Adequate	04/07/05	---
	III			3	Adequate	06/27/03	---
	III				Adequate	pending	---

[1] Action codes for DMF Table:
1 – DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,259	AD-4833MET tablets
IND	33,729	PIO HCl
NDA	21-073	Actos® (PIO HCl tablets)
NDA	20-357	Glucophage® (MET HCl tablets)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	---	---
EES	Acceptable	05/18/05	OC
Pharm/Tox	None	---	---
Biopharm	Acceptable	pending	J.Vaidyanathan
LNC	N/A	---	---
Methods Validation	N/A	---	---
OPDRA	N/A	---	---
EA	Acceptable	CMC Review #1	M.Adams
Microbiology	N/A	---	---

19. ORDER OF REVIEW (OGD Only): N/A

The Chemistry Review for NDA 21-842

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application is recommended for APPROVAL with respect CMC information.

B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS

A standard stability commitment is made.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

ACTOPLUS MET™ is 15 mg Pioglitazone (as HCl salt) + 500 mg Metformin HCl [15+500 tablets] formulated as white to off-white, 8.7 mm x 13.7 mm, film-coated, immediate release tablets debossed "15/500" and "4833M"; or 15 mg Pioglitazone (as HCl salt) + 850 mg Metformin HCl [15+850 tablets] formulated as white to off-white, 9.7 mm x 17.7 mm, film-coated, immediate release tablets debossed "15/850" and "4833M". The proposed drug product is intended to provide a single tablet with a clinical effect bioequivalent to the administration of two single-entity immediate release tablets of the same dose.

Tablet manufacturing is to be at Takeda Pharmaceutical Co. (Osaka, Japan); [redacted]

[redacted] Each site was found to be in compliance with cGMPs.

Unit dose, pilot-scale and commercial-scale formulations are provided. Commercial scale will be [redacted] units for the 15+500 tablets and [redacted] units for 15+850 tablets. The [redacted] excipients are Microcrystalline Cellulose, Povidone, Croscarmellose Sodium, Magnesium Stearate [redacted] Hypromellose, Polyethylene Glycol 8000, Talc, Titanium Dioxide [redacted] All excipients are USP/NF grade materials. No excipient is of human or animal origin. No novel excipients are used.

During product development it was found that [redacted]. The double entity tablet failed to be bioequivalent to combined single entity products. This problem was resolved by [redacted] The proposed dissolution method was found to be capable of distinguishing between bioequivalent and non-bioequivalent tablet formulations. [redacted] was found to enhance manufacturing efficiency.

Tablet manufacture is by [redacted]

The manufacturing process, process parameters and in-process controls are described in detail and justified by the developmental studies and stability data; master production and executed batch records are included in the application.

Release and stability specifications are the same. They address tablet appearance; identity for each molecular entity; dissolution of each entity by HPLC; assay and content uniformity for each entity by HPLC; identified, unknown and total related substances from each entity by HPLC; and [redacted] The analytical methods are described in detail and are validated. The criteria are justified by batch analysis and stability data from

tablets and experience with bulk drug substance. Potential and observed impurities and degradates for each entity are identified. Sources or mechanisms of formation for each compound are described. Molecular structures are provided for known related substances and those observed at levels over the ICH Q3 threshold. Non-USP reference standards for related substances are identified.

The market configurations will be 60-, — and 180-count in — bottles with — child resistant closures, . The physician sample will be a 14-count blister pack (2x3 and 2x4 arrays on a perforated card representing 3 and 4 day regimens) composed of — aluminum foil blister with aluminum Push-Through-Foil lidding. The packaging components are described in detail and acceptable acceptance specifications are provided. The blister pack forms a USP <671> class A package.

The proposed expiry period is 24 months with storage at USP CRT condition for the 4 packages. This proposal is supported by — long term studies; — accelerated studies; and stress studies addressing light, heat and humidity. The tablet dissolution, Pioglitazone related substance formation, and LOD were adversely affected by heat and humidity. An acceptable post-approval stability protocol with commitments was provided.

The package insert addresses only the 60-count and 180-count market configurations. Labels for bottles, blisters, blister carton, and display tray are provided. The CMC information in these labels and labeling is acceptable and complete.

The applicant has justified their request for categorical exclusion from filing an environmental assessment.

Pioglitazone HCl is currently approved only under Takeda's NDA 21-073 (Actos® tablets). Pioglitazone HCl is a white crystalline powder with very limited solubility in water at pH 2-12 (it is especially low at higher pH) and . Manufacturers of the key intermediate are to be

— Manufacturers of finished drug substance are to be — Takeda Pharmaceutical Co. (Yamaguchi, Japan) and — . Each site was found to be in compliance with cGMPS.

Manufacture is by a —

— A detailed description of the synthesis, process parameters and in-process controls is provided. Bulk drug substance is well characterized; adequate molecular structure proof information is provided; and the impurity profile is well documented.

The acceptance specification includes identity for molecular structure; — known, unidentified and total related substances by — impurities by — assay by — and — The analytical methods are described in detail and are validated. The criteria are justified by historical batch analysis and stability data. The drug substance reference standard is prepared and characterized by the applicant.

Bulk drug substance is stored in A retest period when stored at ICH CRT condition is proposed and supported with data in NDA 21-073. The data includes ICH long term and accelerated stability studies, and stress studies addressing heat, humidity and light.

Metformin HCl is currently approved under multiple NDAs and ANDAs. It is a white crystalline powder that is freely soluble in water It is provided as — The molecule has no — The manufacturer is to be — . CMC information is provided to the application by reference to — type II DMF — The manufacturing site was found to be in compliance with cGMPs.

Manufacture is by a — A detailed description of the synthesis, process parameters and in-process controls is provided in the DMF. Bulk drug substance is well characterized; adequate structure proof information is provided; and the impurity profile is well documented.

The acceptance specification includes identity for molecular structure; — known, unidentified and total related substances by — impurities by — assay by — The analytical methods are described in detail and are validated. The criteria are justified by historical batch analysis and stability data. USP reference standard is available for drug substance and 1 known related substance. The applicant characterizes the reference standards used for the other known related substances.

Bulk drug substance is stored in —. A —etest period when stored at ICH CRT conditions is proposed and supported with data in DMF —. The data includes ICH long term and accelerated stability studies, and stress studies addressing heat, humidity and light

B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

ACTOPLUS MET™ is for the management of type 2 diabetes inadequately controlled by Metformin alone. The drug product is 15 mg Pioglitazone (formulated as HCl salt) + 500 mg Metformin HCl and 15 mg Pioglitazone (formulated as HCl salt) + 850 mg Metformin HCl formulated as debossed, white to off-white, oblong, film-coated, immediate release tablets. Tablets are to be taken orally with water with a maximum recommended daily dose of 45 mg for Pioglitazone and 2550 mg Metformin HCl (3 tablets).

Tablets are provided as physician sample and market package configurations. The physician sample is a blister card (2x4 tablets and 2x3 tablets) in a paperboard carton which represent a 4-day and a 3-day supply of the drug product. The market packages are 60-count, — and 180-count HDPE bottles with — and child resistant closure. Labels and labeling are provided only for the 60-count and 180-count packages. The initial expiry period is 24 months when stored at USP controlled room temperature in a tight container protected from moisture and humidity.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is recommended for APPROVAL with respect to CMC information in that all relevant CMC issues have been satisfactorily addressed in the application.

III. ADMINSITRATIVE

A. REVIEWER'S SIGNATURE

_____

William M. Adams, CMC Reviewer for DMEDP

B. ENDORSEMENT BLOCK

M.Adams/CMC Reviewer for HFD-510
S.Moore/CMC TL for HFD-510
J.Weber/PM

C. CC BLOCK

87 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

/s/

Mike Adams
7/20/05 04:39:41 PM
CHEMIST

Stephen Moore
7/20/05 04:56:55 PM
CHEMIST