

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

22-024

**CHEMISTRY REVIEW(S)**

**ActoPlus MET™ XR**  
**(pioglitazone HCl/metformin HCl extended release)**  
**Tablets**  
**NDA 22-024**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Takeda Global Research & Development Center, Inc.  
475 Half Day Road  
Lincolnshire, IL 60069

**Indication:** Adjunct to diet and exercise as a once daily, fixed dose, combination therapy to improve glycemic control in patients with type 2 diabetes mellitus.

**Presentation:** The drug product is supplied in two strengths, either 15 mg pioglitazone/1000 mg metformin or 30 mg pioglitazone/1000 mg metformin, as extended release tablets and is packaged in 30, 60, and 90-count HDPE bottles, with desiccant, as market packages or (b) (4) as physician samples.

**EER Status:** Withhold 18-Jul-2006

**Consults:** Pharm/Tox – Acceptable (cf. NDA 21-073 and 21-574)  
ClinPharm - Acceptable 4-Jan-2007  
Methods Validation – Method validation package is provided. Samples will be requested for method validation study to be conducted by FDA laboratories.  
EA – Categorical exclusion granted under 21 CFR §25.31(a) for both drugs  
DMETS – Acceptable 8-JAN-2007

**Original Submission:** 31-Mar-2006

**Amendments:** 03-Nov-2006  
30-Nov-2006

**Post-Approval Agreements:** None

**Drug Substances:**

**Pioglitazone HCl**

Pioglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ). Activation of PPAR $\gamma$  nuclear receptors regulates the transcription of insulin-related genes involved in the control of glucose production, transport, and utilization. Pioglitazone HCl has a chemical name of ( $\pm$ )-5-[[4-[2-(5-Ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride, a molecular formula of C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S • HCl, and molecular weight of 392.90 g/mole. The hydrochloride salt is a white crystalline

powder that is soluble in (b) (4) and slightly soluble in ethanol. Water solubility is pH dependent and is <0.01 mg/mL at physiological pH. The drug molecule is chiral and the racemate is used in the formulation. The drug substance, pioglitazone HCl, is that approved for use in NDA 21-073 for Takeda's Acto® tablets and reference is made to such and its supplements for all chemistry, manufacturing, and controls information pertaining to pioglitazone HCl.

The release specifications include appearance, identity, assay, related impurities, heavy metals, residual solvents, moisture content, and particle size distribution. The proposed regulatory methods have been validated. The reference standard, a (b) (4) commercial lot, has been developed, characterized, and purity data provided.

Bulk pioglitazone HCl, packed in (b) (4) inside a (b) (4) is stable for up to 4 years when stored at room temperature (25°C/60 %RH) or up to 6 months when stored at elevated temperature (40°C/75%RH).

### Metformin HCl

Metformin is a biguanide class of antihyperglycemic agent that acts primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Metformin HCl has a chemical name of 1,1-Dimethylbiguanide hydrochloride, a molecular formula of  $C_4H_{11}N_5 \cdot HCl$ , and a molecular weight of 165.62 g/mole.

CMC information on the drug substance, metformin HCl, is described in the Type II DMF (b) (4) detailed information on manufacture, in-process controls, analytical procedures and their validation, and stability is included. The applicant has summarized information regarding nomenclature, general properties, manufacturing sites, acceptance specifications, reference standard, batch analysis data, structural elucidation, and stability studies in the NDA.

The release specifications include description, identification, loss on drying, residue on ignition, heavy metal, assay, related impurities, residual solvents and particle size. These specifications comply with the USP monograph for metformin hydrochloride. The drug substance specification differs from the USP monograph in (b) (4). The reference standard for metformin HCl is commercially available from USP.

Bulk metformin HCl, packed in (b) (4) inside a (b) (4), is stable for up to 5 years at room temperature (25°C/60% RH) or at elevated temperature (40°C/75% RH).

**Conclusion:** Drug substance information is acceptable.

**Drug Product:**

The drug product is a fixed dose combination tablet, composed of a metformin HCl extended release core that is coated with an immediate release pioglitazone HCl formulation, and is available as two strengths with the following description:

The 15/1000 tablets contain 15 mg pioglitazone /1000 metformin mg, are white to off-white film-coated, round tablets imprinted with "4833X" and "15/1000" in red on one side, and weigh 1255 mg.

The 30/1000 tablets contain 30 mg pioglitazone /1000 metformin mg, are white to off-white film-coated, round tablets imprinted with "4833X" and "30/1000" in light blue on one side, and weigh 1291 mg.

Manufacture of the drug product utilizes Andrx's propriety Single Composition Osmotic Tablet (SCOT) delivery technology which, in this case, consists of a metformin HCl extended-release core that is coated with an immediate-release pioglitazone HCl formulation.



(b) (4)

The specification for the drug product includes description, identification (HPLC, TLC), assay (HPLC), content uniformity, drug release (dissolution), loss on drying, and related compounds. The proposed regulatory methods have been validated. The drug product reference materials are the same as those used for pioglitazone HCL and metformin HCL drug substances.

Stability data indicate that there are no significant changes in terms of description, assay, related compounds, dissolution, loss on drying, and microbial limits when tablets are stored under either long-term (25°C/60%) or accelerated (40°C/75%RH) conditions in HDPE bottles with closure and desiccant pack and in (b) (4). Photostability studies indicate no significant changes for known pioglitazone impurities and metformin impurities. However, pioglitazone unknown impurities increased slightly upon exposure to light. At high temperature and low humidity, all results met specification.

Based on 12 months of stability data for tablets packaged in HDPE bottles and blister packages stored under long-term and accelerated conditions, the requested expiration dating period of 24 months is acceptable.

**Conclusion:** Drug product information is acceptable.

**Additional Items:**

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

The applicant agrees to place one batch annually in the post-approval stability program.

A satisfactory response to the CMC labeling comments is pending. Strengths for Pioglitazone as free base and metformin as free base appear on label; label strengths should agree with the established names pioglitazone HCl and metformin HCl.

**Overall Conclusion:**

From a CMC perspective, the application is **Approvable** because of **Withhold** recommendation from Office of Compliance.

Blair A. Fraser, Ph.D.  
Director  
DPA I/ONDQA

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Blair Fraser  
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CHEMIST

**NDA 22-024**

**ACTOPLUS MET™ XR**  
**(pioglitazone HCl/metformin HCl**  
**extended-release)**  
**Tablets**

**Takeda**

**Chien-Hua Niu, Ph.D.**  
**ONDQA/DPMA-I**

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# Chemistry Review Data Sheet

1. **NDA 22-024**
2. REVIEW #: 2
3. REVIEW DATE: February 1, 2007
4. REVIEWER: Chien-Hua Niu, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission Type	Document Date
Amendment	03-NOV-2006
Amendment	30-NOV-2006

7. NAME & ADDRESS OF APPLICANT:

**Name:** Takeda Global Research and Development Center, Inc.  
**Address:** One Takeda Parkway  
Deerfield, IL 60015-2235

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ACTOPLUS MET™ XR
- b) Non-Proprietary Name (USAN): Pioglitazone HCl  
: Metformine HCl
- c) Code Name/# (ONDC only): 112529-15-4 (CAS registry number for Pioglitazone)  
1115-70-4 (CAS registry number for Metformine)
- d) Type/Submission Priority (ONDC only):
  - Chem. Type:
  - Submission Priority: **1 S**

## Chemistry Review Data Sheet

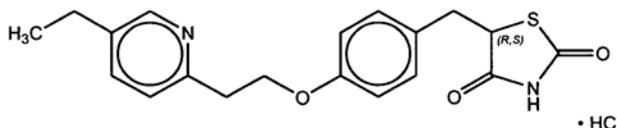
9. LEGAL BASIS FOR SUBMISSION: Not applicable
10. PHARMACOL. CATEGORY: Antihyperglycemic agent
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 15 mg pioglitazone/1000 mg metformin ER  
30 mg pioglitazone/1000 mg metformin ER
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):  
 SPOTS product – Form Completed  
 Not a SPOTS product

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

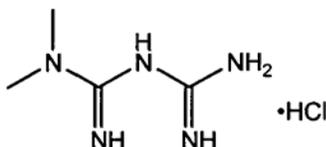
Chemical Name: (±)-5-[[4-[2-(5-Ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride (Pioglitazone HCl)

1,1-Dimethylbiguanide hydrochloride (Metformin HCl)

Structural Formula: Pioglitazone HCl



Metformin HCl



Molecular Formula: Pioglitazone HCl:  $C_{19}H_{20}N_2O_3S \cdot HCl$

Metformin HCl:  $C_4H_{11}N_5 \cdot HCl$

Molecular Weight: Pioglitazone HCl: 392.90 g/mol

Metformin HCl: 165.62

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	11-July -06	Reviewed by Chien-Hua Niu for NDA #22-024
	IV			1	Adequate	10-October-06	Reviewed by Chien-Hua Niu for NDA #22-024
	III			3	Adequate	07-August-06	Reviewed by Josephine Jee for NDA #21-991
	III			3	Adequate	07-December-04	Reviewed by Rapti Madurawe for IND (b) (4)
	III			3	Adequate	01-August-06	Reviewed by Josephine Jee for NDA 21-991
	III			3	Adequate	07-January-04	Reviewed by Monica Cooper for NDA 13-174
	III			3	Adequate	23-June-06	Reviewed by Josephine Jee for NDA #21-991
	III			3	Adequate		Reviewed by Mike Adam for NDA #21-925
	III			3	Adequate		Reviewed by Shulin Ding for NDA (b) (4)

<sup>1</sup> 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")

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

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,462	Antihyperglycemic Agent

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Required		
EES	Pending		Office of Compliance
Pharm/Tox	Acceptable (see NDA #21-073 and NDA #21-574)		Karen David-Bruno
Biopharm	Acceptable	12/27/06	Jayabharathi Vaidyanathan
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Chien-Hua Niu
DMETS	Acceptable	01/08/07	Kanika Vij
EA	Categorical exclusion		Chien-Hua Niu

## REVIEW NOTE

# The Chemistry Review for NDA 22-024

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is **approvable**, pending an acceptable establishment evaluation by the Office of Compliance for the manufacturing sites for the drug product at Andrx Pharmaceutical Inc.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

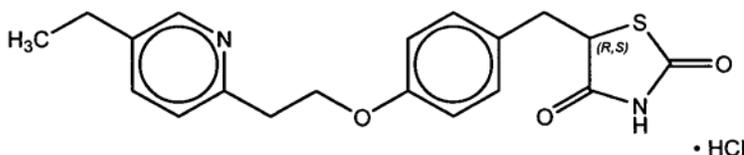
**Pioglitazone** is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ). Activation of PPAR $\gamma$  nuclear receptors regulates the transcription of insulin-related genes involved in the control of glucose production, transport, and utilization.

**Metformin** is an antihyperglycemic agent that belongs to the biguanide class. Their mode of action is that biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis.

When taken in combination, pioglitazone and metformin together, provide additive benefits and lead to improved glycemic control in patient with type 2 diabetes mellitus.

#### DRUG SUBSTANCE:

##### Pioglitazone HCl



All respective CMC information for pioglitazone HCl drug substance is contained with NDA 21-073 for ACTO tablets, and its related amendments and annual reports. Reference is also made to S-006, S-015 and S-019 to this NDA for CMC information on alternate drug substance suppliers. Brief summaries of the information are provided in this application, including nomenclature, general properties, manufacturing processes and in-process

## REVIEW NOTE

controls, manufacturing and control sites, structural characterization, acceptance specifications, reference standards, batch analysis data, and stability studies.

The manufacturing process for pioglitazone HCl is involved in two main stages. The first

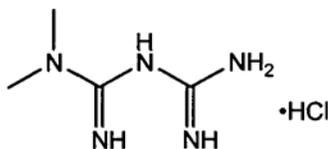
(b) (4)

The release specifications include appearance, identity, assay, related impurities, heavy metals, residual solvents, moisture content, and particle size distribution. Analytical methods and their validation studies are summarized. Reference standard, a (b) (4) commercial lot, is identified and purity data is provided.

The drug product manufacturer (Andrx Pharmaceuticals) will also analyze each receipt of drug substance in conformance with in-house specifications. These in-house specifications are the same as the drug substance manufacturer's specifications except for the unit of measure (b) (4) for the residual solvent test and the addition of an identity test for the (b) (4).

Based on data from ICH stability studies on three (3) commercial lots, pioglitazone HCl is stable for up to five years at room temperature when stored in (b) (4) in (b) (4) at 25°C/60 %RH for a period of up to 48 months and 40°C/75%RH (6 months).

**Metformin HCl** is designated chemically as 1,1-dimethylbiguanide hydrochloride. The chemical structure and molecular formula for metformin HCl are shown below:



All CMC information on metformin HCl is referred to (b) (4) Type II DMF # (b) (4). The applicant has summarized information regarding nomenclature, general properties, manufacturing sites, acceptance specifications, reference standard, batch analysis data, structural elucidation, and stability studies in NDA submission. Detailed information on manufacture, in-process controls, analytical procedures and their validation, and stability is included in the approved DMF (b) (4).

Metformin HCl is manufactured and controlled at one site (b) (4).

The release specifications include description, identification, LOD, residue in ignition, heavy metal, assay, related impurities, residual solvents and particle size. These specifications were recently revised to comply with the new USP monograph for metformin hydrochloride (see Chem. Rev. #9 for DMF (b) (4)).

## REVIEW NOTE

Compared to the current USP monograph for metformin hydrochloride, the drug substance specification implemented by the drug substance manufacturer (b) (4) has two differences: (b) (4)

The reference standard for metformin HCl is commercially available from USP and EP. The current USP reference standard Lot # for metformin HCl is H0E136 (cat. #: 1396309).

Metformin HCl is (b) (4) inside (b) (4) and sealed. The (b) (4) are then stored inside of a (u) (+).

Results of the stability studies of Lot CH7149 demonstrate that there have been no indications of a decrease in quality or loss in potency in metformin HCl stored for up to 60 months at 25°C/60% RH and 40°C/75% RH.

**DRUG PRODUCT:** The proposed drug product, ACTOPILUS MET XT, is manufactured by Andrx Pharmaceuticals Inc. (4955 Orange DR. Ft. Lauderdale, FL 33314). The drug product is a fixed dose combination tablet composed of a metformin HCl extended release core coating with an immediate release pioglitazone HCl formulation. The two AD-4833XT tablet strengths are shown below grade:

Strength	Description
15 mg/1000 mg	Round white to off-white filmed coated tablet imprinted with "4833X" and "15/1000" in red on one side
30 mg/1000 mg	Round white to off-white filmed coated tablet imprinted with "4833X" and "30/1000" in light blue on one side

The core tablet dosage form (metformin extended-release formulation) utilizes Andrx's proprietary Single Composition Osmotic Tablet (SCOT) delivery technology. These Metformin XT laser drilled tablets are manufactured by the same manufacturing process as described in the approved NDA #21-574 for FORTAMET.

(b) (4)

The manufacturing process and in-process controls are described in detail.

Both strengths of AD-4833XT tablets are packaged in HDPE bottles (30-, 60-, and 90-count) with child-resistant closure for commercial distribution and (b) (4) packages for the physician samples.

## REVIEW NOTE

The proposed release specifications include description, identification (HPLC, TL), assay (HPLC), content uniformity, drug release (dissolution), loss on drying, and related compounds. The proposed regulatory methods have been validated.

The dissolution test of AD-4833XT tablets was conducted under two sets of conditions.  
(b) (4)

Stability tests performed include description, assay, related compounds, dissolution, loss on drying, and microbial limits.

DA-4833XT tablets packaged in HDPE bottles with CRC closure, desiccant pack and (b) (4) show no significant changes in terms of description, assay, related compounds, dissolution, loss on drying, and microbial limited when store at long-term conditions (25°C/60%) and accelerated conditions (40°C/75%RH). The photostability study indicates that no significant concentration change for pioglitazone known impurities (b) (4) or metformin impurities (b) (4) were observed. However, pioglitazone unknown impurities increased with exposure to light. At high temperature and low humidity, all results met proposed specifications.

Based on 12 months of stability data from samples packaged HDPE bottles and (b) (4) stored at ICH long-term and accelerated conditions, an expiration dating period of 24 months requested by the firm is acceptable for AD-4833XT tablets.

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.

**B. Description of How the Drug Product is Intended to be Used**

ACTOPLUS MET™ XR consists of metformin extended-release core coated tablet with an immediate-release pioglitazone layer used in the management of type 2 diabetes. The firm indicates that the recommended dosage of ACTOPLUS MET is 15 mg pioglitazone HCl (as free base) with 1000 mg metformin HCl (15 mg/1000 mg) or 30 mg pioglitazone HCl and 1000 mg metformin HCl (30 mg/1000 mg) administered once-a-day.

## REVIEW NOTE

## C. Basis for Approvability or Not-Approval Recommendation

The recommendation that this application is **approvable** from a CMC viewpoint is based on the following: (1) The CMC information on the drug substance, including pioglitazone HCl and metformin HCl, has been thoroughly reviewed for NDA #21-073 (ACTO tablets) and NDA #21-574 (FORTAMET XT), respectively and found adequate to support the application of NDA #22-024. (2) The two ACTOPLUS MET XT tablet strengths, 15 mg/1000 mg and 30 mg/1000 mg, were manufactured using SCOT delivery technology to prepare the metformin core tablets and then by (b) (4) of the pioglitazone immediate-release formulation on the metformin core. The manufacturing process and in-process controls are validated. However, a number of chemistry non-approvability requests for information on the in-process controls are being made. (3) Three primary stability batches for each dose strengths have been manufactured by Andrx Pharmaceuticals Inc. at 4955 Orange Dr., Ft Lauderdale, FL 33314. Both strengths of tablets are packaged in HDPE bottles with CRC caps and (b) (4). (4) Stability data indicate that no significant changes were observed in terms of description, assay, related compounds, dissolution, loss on drying, and microbial limits when stored at 25°C/60% RH and 40°C/75% RH for a period of up to 12 months. and (5) Satisfactory response to IR letter.

**Pending Issue:** (1). The satisfactory recommendation issued by the Office of Compliance for the manufacturing sites for the drug product at Andrx Pharmaceutical Inc.

## III. Administrative

## A. Reviewer's Signature

## B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I

Chemistry Division Director: Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-I

## C. CC Block

Dr. Blair Fraser/Dr. Su (Suong) Tran

Project Manager Name/Date: Jena Weber, OND/HFD-510

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Chien-Hua Niu  
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Blair Fraser  
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CHEMIST

**NDA 22-024**

**ACTOPLUS MET™ XR**  
**(pioglitazone HCl/metformin HCl**  
**extended-release)**  
**Tablets**

**Takeda**

**Chien-Hua Niu, Ph.D.**  
**ONDQA/DPMA-I**

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# Chemistry Review Data Sheet

1. **NDA 21-912**

2. REVIEW #: 1

3. REVIEW DATE: October 13, 2006

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission Type	Document Date
Original	31-MAR-2006

7. NAME & ADDRESS OF APPLICANT:

**Name:** Takeda Global Research and Development Center, Inc.  
**Address:** 475 Half Day Road  
Lincolnshire, IL 60069

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ACTOPLUS MET™ XR

b) Non-Proprietary Name (USAN): Pioglitazone HCl  
: Metformine HCl

c) Code Name/# (ONDC only): 112529-15-4 (CAS registry number for Pioglitazone)  
1115-70-4 (CAS registry number for Metformine)

d) Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: **1 S**

## Chemistry Review Data Sheet

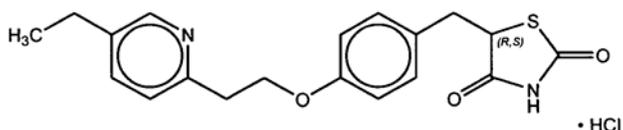
9. LEGAL BASIS FOR SUBMISSION: Not applicable
10. PHARMACOL. CATEGORY: Antihyperglycemic agent
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 15 mg pioglitazone/1000 mg metformin ER  
30 mg pioglitazone/1000 mg metformin ER
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):  
 SPOTS product – Form Completed  
 Not a SPOTS product

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

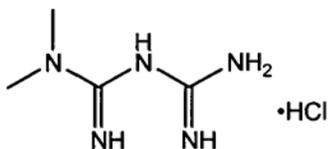
Chemical Name: (±)-5-[[4-[2-(5-Ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride (Pioglitazone HCl)

1,1-Dimethylbiguanide hydrochloride (Metformin HCl)

Structural Formula: Pioglitazone HCl



Metformin HCl



Molecular Formula: Pioglitazone HCl:  $C_{19}H_{20}N_2O_3S \cdot HCl$   
Metformin HCl:  $C_4H_{11}N_5 \cdot HCl$

Molecular Weight: Pioglitazone HCl: 392.90 g/mol  
Metformin HCl: 165.62

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Metformin HCl	1	Adequate	11-July -06	Reviewed by Chien-Hua Niu for NDA #22-024
	IV	(b) (4)	(b) (4)	1	Adequate	10-October-06	Reviewed by Chien-Hua Niu for NDA #22-024
	III	(b) (4)	(b) (4)	3	Adequate	07-August-06	Reviewed by Josephine Jee for NDA #21-991
	III	(b) (4)	(b) (4)	3	Adequate	07-December-04	Reviewed by Rapti Madurawe for IND (b) (4)
	III	(b) (4)	(b) (4)	3	Adequate	01-August-06	Reviewed by Josephine Jee for NDA 21-991
	III	(b) (4)	(b) (4)	3	Adequate	07-January-04	Reviewed by Monica Cooper for NDA 13-174
	III	(b) (4)	(b) (4)	3	Adequate	23-June-06	Reviewed by Josephine Jee for NDA #21-991
	III	(b) (4)	(b) (4)	3	Adequate		Reviewed by Mike Adam for NDA #21-925
	III	(b) (4)	(b) (4)	3	Adequate	10-July-06	Reviewed by Shulin Ding for NDA (b) (4)

<sup>1</sup> 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")

<sup>2</sup> 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	68,462	Antihyperglycemic Agent

Chemistry Review Data Sheet

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	Not Required		
EES	Pending		Office of Compliance
Pharm/Tox	Pending		Karen David-Bruno
Biopharm	Pending		Jayabharathi Vaidyanathan
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Chien-Hua Niu
DMETS	Pending		Diane Smith
EA	Categorical exclusion		Chien-Hua Niu

## REVIEW NOTE

# The Chemistry Review for NDA 21-912

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application can be approved from chemistry point of view.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

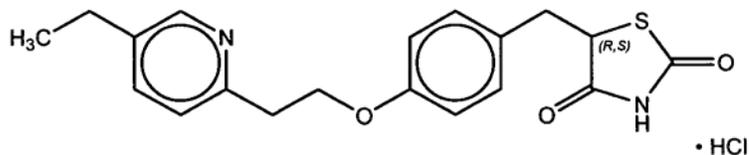
**Pioglitazone** is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ). Activation of PPAR $\gamma$  nuclear receptors regulates the transcription of insulin-related genes involved in the control of glucose production, transport, and utilization.

**Metformin** is an antihyperglycemic agent that belongs to the biguanide class. Their mode of action is that biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis.

When taken in combination, pioglitazone and metformin together, provide additive benefits and lead to improved glycemic control in patient with type 2 diabetes mellitus.

#### DRUG SUBSTANCE:

##### Pioglitazone HCl



All respective CMC information for pioglitazone HCl drug substance is contained with NDA 21-073 for ACTO tablets, and its related amendments and annual reports. Reference is also made to S-006, S-015 and S-019 to this NDA for CMC information on alternate drug substance suppliers. Brief summaries of the information are provided in this application, including nomenclature, general properties, manufacturing processes and in-process controls, manufacturing and control sites, structural characterization, acceptance specifications, reference standards, batch analysis data, and stability studies.

## REVIEW NOTE

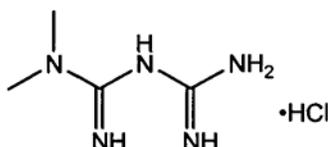
The manufacturing process for pioglitazone HCl is involved in two main stages. The first stage (b) (4)

The release specifications include appearance, identity, assay, related impurities, heavy metals, residual solvents, moisture content, and particle size distribution. Analytical methods and their validation studies are summarized. Reference standard, a (b) (4) commercial lot, is identified and purity data is provided.

The drug product manufacturer (Andrx Pharmaceuticals) will also analyze each receipt of drug substance in conformance with in-house specifications. These in-house specifications are the same as the drug substance manufacturer's specifications except for the unit of measure (b) (4) for the residual solvent test and the addition of an identity test for the (b) (4).

Based on data from ICH stability studies on three (3) commercial lots, pioglitazone HCl is stable for up to five years at room temperature when stored in (b) (4) in (b) (4) at 25°C/60 %RH for a period of up to 48 months and 40°C/75%RH (6 months).

**Metformin HCl** is designated chemically as 1,1-dimethylbiguanide hydrochloride. The chemical structure and molecular formula for metformin HCl are shown below:



All CMC information on metformin HCl is referred to (b) (4) Type II DMF (b) (4). The applicant has summarized information regarding nomenclature, general properties, manufacturing sites, acceptance specifications, reference standard, batch analysis data, structural elucidation, and stability studies in NDA submission. Detailed information on manufacture, in-process controls, analytical procedures and their validation, and stability is included in the approved DMF (b) (4).

Metformin HCl is manufactured and controlled at one site ( (b) (4) )

The release specifications include description, identification, LOD, residue in ignition, heavy metal, assay, related impurities, residual solvents and particle size. These specifications were recently revised to comply with the new USP monograph for metformin hydrochloride (see Chem. Rev. #9 for DMF (b) (4)).

**REVIEW NOTE**

Compared to the current USP monograph for metformin hydrochloride, the drug substance specification implemented by the drug substance manufacturer (b) (4) has two differences: (b) (4)

[Redacted]

The reference standard for metformin HCl is commercially available from USP and EP. The current USP reference standard Lot # for metformin HCl is H0E136 (cat. #: 1396309).

Metformin HCl is (b) (4) inside (b) (4) bags and sealed. The LDPE bags are then stored inside of a fiberboard drum.

Results of the stability studies of Lot CH7149 demonstrate that there have been no indications of a decrease in quality or loss in potency in metformin HCl stored for up to 60 months at 25°C/60% RH and 40°C/75% RH.

**DRUG PRODUCT:** The proposed drug product, ACTOPILUS MET XT, is manufactured by Andrx Pharmaceuticals Inc. (4955 Orange DR. Ft. Lauderdale, FL 33314). The drug product is a fixed dose combination tablet composed of a metformin HCl extended release core coating with an immediate release pioglitazone HCl formulation. The two AD-4833XT tablet strengths are shown below grade:

<b>Strength</b>	<b>Description</b>
15 mg/1000 mg	Round white to off-white filmed coated tablet imprinted with "4833X and "15/1000" in red on one side
30 mg/1000 mg	Round white to off-white filmed coated tablet imprinted with "4833X" and "30/1000" in light blue on one side

The core tablet dosage form (metformin extended-release formulation) utilizes Andrx's propriety Single Composition Osmotic Tablet (SCOT) delivery technology. These Metformin XT laser drilled tablets are manufactured by the same manufacturing process as described in the approved NDA #21-574 for FORTAMET.

[Redacted] (b) (4)

The manufacturing process and in-process controls are described in detail.

Both strengths of AD-4833XT tablets are packaged in HDPE bottles (30-, 60-, and 90-count) with child-resistant closure for commercial distribution (b) (4)

[Redacted]

## REVIEW NOTE

The proposed release specifications include description, identification (HPLC, TL), assay (HPLC), content uniformity, drug release (dissolution), loss on drying, and related compounds. The proposed regulatory methods have been validated.

The dissolution test of AD-4833XT tablets was conducted under two sets of conditions.

(b) (4)

Stability tests performed include description, assay, related compounds, dissolution, loss on drying, and microbial limits.

DA-4833XT tablets packaged in HDPE bottles with CRC closure, desiccant pack and (b) (4) show no significant changes in terms of description, assay, related compounds, dissolution, loss on drying, and microbial limited when store at long-term conditions (25°C/60%) and accelerated conditions (40°C/75%RH). The photostability study indicates that no significant concentration change for pioglitazone known impurities (b) (4) and (b) (4) or metformin impurities (b) (4) and (b) (4) were observed. However, pioglitazone unknown impurities increased with exposure to light. At high temperature and low humidity, all results met proposed specifications.

Based on 6 months of stability data from samples packaged HDPE bottles and (b) (4) stored at ICH long-term and accelerated conditions, an expiration dating period of 24 months requested by the firm cannot be recommended for AD-4833XT tablets until additional stability data are provided and evaluated.

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.

## B. Description of How the Drug Product is Intended to be Used

ACTOPLUS MET™ XR consists of metformin extended-release core coated tablet with an immediate-release pioglitazone layer used in the management of type 2 diabetes. The firm indicates that the recommended dosage of ACTOPLUS MET is 15 mg pioglitazone HCl (as free base) with 1000 mg metformin HCl (15 mg/1000 mg) or 30 mg pioglitazone HCl and 1000 mg metformin HCl (30 mg/1000 mg) administered once-a-day.

## C. Basis for Approvability or Not-Approval Recommendation

The recommendation that this application is can be **approved** from a CMC viewpoint is based on the following: (1) The CMC information on the drug substance, including pioglitazone HCl and metformin HCl, has been thoroughly reviewed for NDA #21-

**REVIEW NOTE**

073 (ACTO tablets) and NDA #21-574 (FORTAMET XT), respectively and found adequate to support the application of NDA #22-024. (2) The two ACTOPLUS MET XT tablet strengths, 15 mg/1000 mg and 30 mg/1000 mg, were manufactured using SCOT delivery technology to prepare the metformin core tablets and then by (b) (4) of the pioglitazone immediate-release formulation on the metformin core. The manufacturing process and in-process controls are validated. However, a number of chemistry non-approvability requests for information on the in-process controls are being made. (3) Three primary stability batches for each dose strengths have been manufactured by Andrx Pharmaceuticals Inc. at 4955 Orange Dr., Ft Lauderdale, FL 33314. Both strengths of tablets are packaged in HDPE bottles with CRC caps for and (4) Stability data indicate that no significant changes were observed in terms of description, assay, related compounds, dissolution, loss on drying, and microbial limits when stored at 25°C/60% RH and 40°C/75% RH for a period of 6 months. The firm commits to provide the 12 month stability data to support the proposed expiration dating of 24 months for ACTOPLUS MET XT tablets.

**Pending Issue:** (1). The satisfactory recommendation issued by the Office of Compliance for the manufacturing sites for the drug product at Andrx Pharmaceutical Inc.; (2). Submission of additional stability data requested by the Agency on June 14, 2006 facsimile; and (3) Satisfactory response to IR letter.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I

Chemistry Branch Chief Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-I

**C. CC Block**

Dr. Blair Fraser/Dr. Su (Suong) Tran

Project Manager Name/Date: Jena Weber, OND/HFD-510

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

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Chien-Hua Niu  
10/31/2006 10:08:07 AM  
CHEMIST

Blair Fraser  
10/31/2006 01:15:10 PM  
CHEMIST