CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-925

CHEMISTRY REVIEW(S)

Duetact®
(Pioglitazone HCl + Glimiperide)
Immediate Release Tablets
NDA 21-925

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls
Summary #2

Applicant: Takeda Global Research & Development Center, Inc.
475 Half Day Road
Lincolnshire, IL 600069

Indication: Adjunct to diet and exercise as a once daily, fixed combination therapy to improve glycemic control in patients with type 2 diabetes who are already being treated with a combination of thiazolidinedione (Pioglitazone as HCl salt) and sulfonylurea (Glimepiride) or whose diabetes is not adequately controlled with sulfonylurea alone.

Presentation: Immediate release, round, uncoated, bilayer tablets (Pioglitazone on one side and Glimepiride on the other) packaged in 30- and 90- count —— bottles with dessicant.

—— combination tablet strengths available are: 30mg Pioglitazone + 2mg Glimepiride [30+2]; 30mg + 4mg [30+4]; ——

EER Status: **Acceptable** 28-Feb-2006

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(a) for both drugs
Methods Validation – Revalidation by Agency not requested

Original Submission: 28-Jun-2005
Amendments: 12-Dec-2005 (stability update)
20-Apr-2006 (bioequivalence study)

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

Drug Substances:
Pioglitazone is an oral antidiabetic agent (thiazolidinedione) which increases muscle sensitivity to insulin. The hydrochloride salt is a white crystalline powder that is soluble in methanol and slightly soluble in ethanol. Water solubility is pH dependent and is —— ng/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 Actos® 15mg, 30mg,

45mg tablets. Reference is made to NDA 21-073 for all chemistry, manufacturing, and controls information pertaining to pioglitazone HCl for NDA 21-925.

Glimiperide is a sulfonylurea compound which lowers blood glucose levels by stimulation of insulin release from functioning pancreatic beta cells. It is a white crystalline powder that is soluble in water at physiological pH and very slightly soluble in methanol. A [redacted] is used in the formulation. The drug substance is provided by [redacted] and reference is made to the type [redacted] DMF [redacted] for all chemistry, manufacturing and controls information for NDA 21-925.

Conclusion: Drug substance information is acceptable.

Drug Product:

The drug product, Duetact® is an immediate release tablet, described in the application as a round, white to off-white, bilayer, uncoated tablet debossed with "30+2", 30+4" [redacted] representing the tablet strength and "4833G" representing the fixed combination product. The Pioglitazone layer was formulated to [redacted] The Glimepiride layer was formulated to [redacted] The proposed storage condition is USP-controlled room temperature with protection from humidity and moisture.

Conclusion: Drug product information is satisfactory.

Additional Items:

Review of the original application resulted in no CMC deficiencies.

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

The application was amended on 20-Apr-2006 to include:

- [redacted]
  (See Recommendation in OCPB Review #2)
- tightening the dissolution specification for pioglitazone for all [redacted] tablet strengths.
- [redacted]
- changing the trade name to Duetact™ (revised labels and labeling are **Adequate** for CMC content)

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**.

Include the following in the letter to the sponsor.

1. Adequate stability data were provided to support an expiration date of **18 months** for drug product packaged in the —— bottles with desiccant when stored at room temperature.

2. Pending resolution of the issues regarding bioavailability of fresh *versus* aged tablets stored in the bottle configuration, we recommend
   a. the proposed expiry period not be extended beyond **18 months**; and
   b. comparative dissolution profiles alone not be considered as sufficient to support CMC changes which may affect drug product bioavailability.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
7/13/2006 03:40:58 PM
CHEMIST

Chi Wan Chen
7/27/2006 05:51:54 PM
CHEMIST

[redacted] (30 mg pioglitazone + 2 mg glimiperide, 30 mg pioglitazone + 4 mg glimiperide, [redacted]) Immediate Release Tablets

NDA 20-925

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 600069

Indication: An adjunct to diet and exercise as a once daily fixed combination therapy to improve glycemic control in patients with type 2 diabetes who are already being treated with a combination of thiazolidinedione (Pioglitazone as HCl salt) and sulfonylurea (Glimepiride) or whose diabetes is not adequately controlled with sulfonylurea alone.

Presentation: Immediate release, round bilayer tablet (Glimepiride on one side and Pioglitazone on the other side) packaged in a 30- and 90-count [redacted] bottle with dessicant as market package or 7-count aluminum-aluminum push-thru blister pack as physician sample package.

EER Status: Acceptable 28-Feb-2006

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(a) for both drugs
Methods Validation – Revalidation by Agency not requested

Original Submission: 28-Jun-2005
Amendment: 12-Dec-2005 (stability update)

Post-Approval Agreements:

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

Drug Substances:

Pioglitazone is an oral antidiabetic agent (thiazolidinedione) which increases muscel sensitivity to insulin. The hydrochloride salt is a white crystalline powder that is soluble in methanol and slightly soluble in ethanol. Water solubility is pH depended and <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 Actos® 15mg, 30mg, 45mg tablets. Reference is made to NDA 21-073 for all chemistry, manufacturing, and controls information pertaining to pioglitazone HCl for NDA 21-925.

Glimiperide is a sulfonylurea compound which lowers blood glucose levels by stimulation of insulin release from functioning pancreatic beta cells. It is a white

crystalline powder that is soluble in water at physiological pH and very slightly soluble in methanol. [redacted] The drug substance is provided by [redacted], and reference is made to their type [redacted] DMF [redacted] for all chemistry, manufacturing and controls information for NDA 21-925.

Conclusion: Drug substance information is acceptable.

Drug Product:

The drug product, [redacted] is an immediate release tablet, described in the application as a round, white to off-white, bilayer, uncoated tablet debossed with "30+2", 30+4" [redacted] representing the table strength and "4833G" representing the fixed combination product. The applicant provided updated stability data in the 15-Dec-2005 amendment. The Pioglitazone layer was formulated to [redacted] The Glimepiride layer was formulated to [redacted] The proposed storage conditions is USP controlled room temperature with protection from humidity and moisture. Historical observations for Actos® and Amaryl® together with submitted stability data support the proposed expiry dating of 24 months for drug product packaged in the proposed bottle and blister pack configurations.

Conclusion: Drug product information is satisfactory.

Additional Items:

A satisfactory response to the CMC labeling comments is pending.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval, pending a satisfactory response to the labeling comments.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
3/20/2006 09:01:01 AM
CHEMIST

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2 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

NDA 21-925

DUETACT™
(Pioglitazone HCl and Glimepiride tablets)

Takeda Global Research & Development Center, Inc.

William M. Adams
Office of New Drug Quality Assessment
(ONDQA)

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Table of Contents

Chemistry Review Data Sheet

1. NDA 21-925

2. REVIEW #2

3. REVIEW DATE: 12-Jul-2006

4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N-000	28-Jun-2005
N-000 (BC)	15-Dec-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-000 (BB/BL)	07-Feb-2006
N-000 (BL/BZ)	24-Mar-2006
N-000 (AZ)	20-Apr-2006
N-000 (BL)	25-May-2006

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) 383-3739
Fax:	(847) 383-3427

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: DUETACT™
   (b) Non-Proprietary Name (USAN): Pioglitazone HCl + Glimepiride tablets
   (c) Code Name/# (ONDC only): AD-4833SU tablets
   (d) Chem. Type/Submission Priority (ONDC only): 4S

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

10. PHARMACOLOGICAL CATEGORY: treatment of type 2 diabetes mellitus

11. DOSAGE FORM: IR tablet

12. STRENGTH/POTENCY: Pioglitazone HCl + Glimepiride (30mg + 2mg, 30mg + 4mg,

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

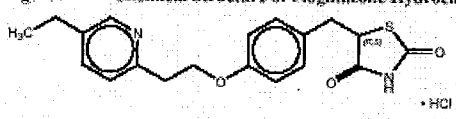
_____SPOTS product – Form Completed

XXX Not a SPOTS product

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

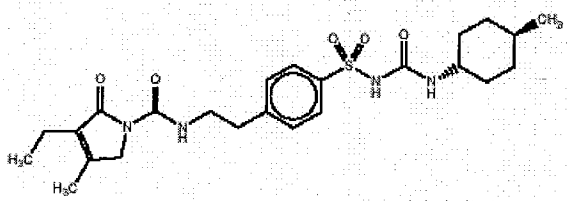
Pioglitazone HCl
Chemical Name: (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monoHCl
Molecular Formula/Weight: $C_{19}H_{20}N_2O_3S$. HCl/ 392.90 amu

Figure 1 Chemical Structure of Pioglitazone Hydrochloride



Glimepiride
Chemical Name: 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl) urea
Molecular Formula/Weight: $C_{24}H_{34}N_4O_5S$/ 490.62 amu

Figure 1 Chemical Structure of Glimepiride



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1				7	Adequate	04/16/04	
2				3			

Chemistry Review Data Sheet

[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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	---	---	---
EES	acceptable	28-Feb-2006	OC
Pharm/Tox			J. El Hage
Biopharm	dissolution procedure & criteria are acceptable	07-Apr-2006	J.A. Vaidyanathan
LNC	---	---	---
Methods Validation	package is provided		W. Adams
OPDRA	---	---	---
EA	accepted in CMC review		W. Adams
Microbiology	---	---	---

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

The Chemistry Review for NDA 21-925

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application is recommended for APPROVAL with respect to CMC information and a comment should be included in the action letter regarding the initial expiry period and the use of comparative dissolution profiles to support CMC changes (see Comments section).

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

No phase 4 commitments are provided in the application.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCT & DRUG SUBSTANCES

DRUG PRODUCT

DUETACT™ is Pioglitazone (as the HCl salt) plus Glimepiride as a white to off-white, round, uncoated, immediate release tablet in — strengths - 30mg Pioglitazone + 2mg Glimepiride [30+2], 30mg Pioglitazone + 4mg Glimepiride [30+4]. — The 30+2 tablet is convex-faced, — diameter, — thick and debossed "30/2" and "4833G". The 30+4 tablet is convex-faced, — diameter, — n thick and debossed "30/4" and "4833G". — The commercial package is 30 or 90 tablets in a — bottle with desiccant. The physician sample is the 30 count commercial package.

This product is intended to be a once-daily dose replacement for two currently approved single-entity drug products. Drug development was based on obtaining a tablet with — ent to Takeda's Actos® (NDA 21-073 for 15mg, 30mg and 45mg Pioglitazone immediate release tablets) and Aventis' Amaryl® (NDA 210-496 for 1mg, 2mg and 4mg Glimepiride tablets).

The formulation and each step of the manufacturing process were investigated with respect to stability, dissolution profiles and manufacturability. — Tablets were found to be moisture sensitive, thus humidity in the manufacturing area was controlled, appropriate packaging systems were selected, and by a test for moisture content was included at tablet release and in the stability protocols.

Tablets will be manufactured and controlled at Takeda Pharmaceutical Company, Ltd (Osaka, Japan) — Stability testing will be performed at —

Manufacture is by a multi-step process —

— Time limits are established for — s and justified with stability studies. No — or — procedures are proposed. Detailed manufacturing instructions, process parameters and in-process controls are provided along with executed batch records for the — lots of each proposed tablet strength used to support the application.

All formulation excipients are USP/NF materials which meet monograph requirements. No excipient is a novel material or of human origin. BSE/TSE issues are adequately addressed for excipients which may be of animal origin. The product release specifications address identity, uniformity, strength, purity and release for each drug substance, and moisture content by loss on drying. Analytical methods are described in detail and validated as

appropriate. Criteria are justified based on batch analysis and stability data obtained on the NDA lots. Impurities observed in the tables are identified by chemical name, molecular structure and mechanism of formation. The analytical methods are shown to quantitate these compounds. The reference standards are those established for drug substance analysis.

The commercial and physician sample packages are a 90cc [redacted] bottle, [redacted] desiccant, [redacted] and [redacted] child resistant closure. The bulk tablet shipping container is a [redacted]. All packaging components are described in detail and qualified for safety, moisture protection and light protection. Component acceptance specifications include tests for identity and dimensions. The commercial package and shipping container both meet USP requirements for a tight container. The desiccant is intended to control relative humidity in the commercial package to within a defined limit.

A detailed description of the post approval stability protocol is provided along with the protocol for the NDA stability studies on [redacted] lots of each tablet strength prepared using [redacted] drug substance lots. The proposed protocol includes a provision for extending the expiry period to [redacted] based on additional data from the NDA studies. Stability studies included unprotected tablets under light, heat and humidity stress conditions; and tablets in bottles, blister packs and the shipping container stored at ICH room temperature and accelerated conditions. Tablets were found to be sensitive to moisture and heat exposure. The submitted study data are considered marginally sufficient to support an initial expiry period of 18 months with storage at USP controlled room temperature and protection from humidity and moisture for tablets in the bottle configurations.

CMC information in the draft package insert, patient information leaflet, bottle labels, and labels for the blister, backing, carton and carton display is adequate and complete. The label storage statement is supported by the stability studies.

The applicant has requested a categorical exclusion under 21 CFR 25.3(a) based on the absence of increased drug substance use since the combination tablet is intended to replace two existing single-entity tablets.

DRUG SUBSTANCE – Pioglitazone HCl

Takeda's NDA 21-073 (Actos® 15mg, 30mg, 45mg tablets) is referenced for all CMC information. The applicant has summarized information regarding nomenclature, general properties, manufacturing processes and in-process controls, manufacturing and control sites, acceptance specifications, reference standards, batch analysis data; bulk shipping and storage containers, and the stability studies.

[redacted]

The release specification addresses identity, assay, organic impurities, inorganic impurities, residual solvents, moisture content, and particle size distribution. Analytical methods and their validation studies are summarized. The criteria are justified by batch analysis data on [redacted] commercial lots used to prepare the NDA tablet lots and historical observation. The reference standard, a [redacted] commercial lot, is identified and purity data is provided.

The bulk shipping and storage container is an [redacted]

Stability studies on [redacted] commercial lots in their storage container stored at ICH controlled room temperature and accelerated conditions are summarized and show the material to be stable for [redacted] at USP controlled room temperature.

DRUG SUBSTANCE – Glimepiride

[redacted] s type [redacted] DMF [redacted] is referenced for all CMC information. The applicant has summarized information regarding nomenclature, general properties, manufacturing sites, acceptance specifications, reference standards, batch analysis data, bulk storage and shipping containers, and the stability studies.

Drug substance is manufactured and controlled at one site [redacted]

The acceptance specification addresses identity, assay, organic impurities, inorganic impurities, residual solvents, moisture content, particle size distribution and polymorph identity. Analytical methods and their validation studies are summarized. The criteria are justified by the USP monograph, by batch analysis data on [redacted] commercial lots used to prepare the NDA tablet lots, and by historical observation. The reference standard, a [redacted] commercial lot, is identified and purity data is provided.

The bulk storage and shipping container is an [redacted]

Stability studies on [redacted] commercial lots in their storage container stored at ICH controlled room temperature and accelerated conditions are summarized and show the material to be stable for [redacted] months are USP controlled room temperature.

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

DUETACT™ is indicated as an adjunct to diet and exercise as a once-daily fixed combination therapy to improve glycemic control in patients with type 2 diabetes who are already being treated with a combination of thiazolidinedione (Pioglitazone) and sulfonylurea (Glimepiride) or whose diabetes is not adequately controlled with sulfonylurea alone. The proposed drug product is Pioglitazone (as the HCl salt) plus Glimepiride formulated as 30mg Pioglitazone + 2mg Glimepiride [30+2], 30mg Pioglitazone + 4mg Glimepiride [30+4] [redacted] strengths. The tablets are immediate release, white to off-white, round, un-coated and debossed with the tablet strength ["30+2", "30+4", [redacted] and "4833G". Tablets are to be taken with a glass of water with maximum dose of [redacted]

Tablets are to be provided in commercial package and physician sample configurations. The commercial packages are 30-count and 90-count plastic bottles with desiccant. The physician sample is the 30 count commercial package. Labels and labeling are provided for each configuration. The initial expiry period of 18 months with storage at USP controlled room temperature and protection from moisture and humidity is acceptable.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is recommended for APPROVAL in that the CMC issues have been addressed.

III. ADMINSITRATIVE

A. REVIEWER'S SIGNATURE

_____

William M. Adams, CMC Reviewer for ONDQA

B. ENDORSEMENT BLOCK

M.Adams/CMC Reviewer for ONDQA
S.Moore/PAL for ONDQA

C. CC BLOCK

Chi-wan Chen/ONDQA/dir DPME I
B.Fraser/ONDQA/DPME I/Branch Chief II
S.Goldie/PM for ONDQA

25 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Mike Adams
7/12/2006 06:40:03 PM
CHEMIST

Stephen Moore
7/12/2006 06:47:04 PM
CHEMIST

NDA 21-925

Takeda Global Research & Development Center, Inc.

William M. Adams
Office of New Drug Quality Assessment
(ONDQA)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-925

2. REVIEW #1

3. REVIEW DATE: 14 Mar-2006

4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS:: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-000	28-Jun-2005
N-000	15-Dec-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) 383-3739
Fax:	(847) 383-3427

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: /
   (b) Non-Proprietary Name (USAN): Pioglitazone HCl + Glimepiride tablets
   (c) Code Name/# (ONDC only): AD-4833SU tablets
   (d) Chem. Type/Submission Priority (ONDC only): 4S

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

10. PHARMACOLOGICAL CATEGORY: treatment of type 2 diabetes mellitus

11. DOSAGE FORM: IR tablet

12. STRENGTH/POTENCY: Pioglitazone HCl + Glimepiride (30mg + 2mg, 30mg + 4mg,

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

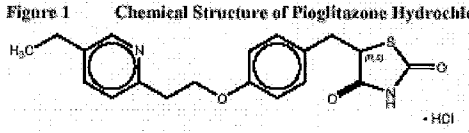
_____SPOTS product – Form Completed

XXX Not a SPOTS product

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

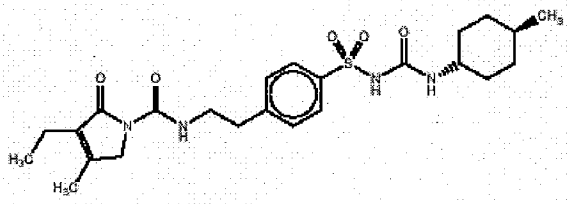
Pioglitazone HCl
Chemical Name: (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monoHCl
Molecular Formula/Weight: $C_{19}H_{20}N_2O_3S$. HCl/ 392.90 amu

Figure 1 Chemical Structure of Pioglitazone Hydrochloride



Glimepiride
Chemical Name: 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl) urea
Molecular Formula/Weight: $C_{24}H_{34}N_4O_5S$/ 490.62 amu

Figure 1 Chemical Structure of Glimepiride



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
					Adequate	04/16/04	

[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: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	---		---
EES	Acceptable	02/28/06	OC
Pharm/Tox			J. El Hage
Biopharm	Dissolution procedure and criteria are accepted	Pending	J.A. Vaidyanathan
LNC	---		---
Methods Validation	Package is provided		W.Adams
OPDRA	---		---
EA	Accepted in CMC review		W. Adams
Microbiology	---		---

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

The Chemistry Review for NDA 21-925

The Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application is recommended for APPROVAL with respect to CMC information.

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

No phase 4 commitments are provided in the application.

II. SUMMARY OF CHEMISTRY ASSESSMENTS

A. DESCRIPTION OF THE DRUG PRODUCTS & DRUG SUBSTANCES

DRUG PRODUCT

[redacted] is Pioglitazone (as the HCl salt) plus Glimepiride as white to off-white, round, uncoated, immediate release tablets in [redacted] strengths - 30mg Pioglitazone + 2mg Glimepiride [30+2], 30mg Pioglitazone + 4mg Glimepiride [30+4] [redacted]. The 30+2 tablet is convex-faced, [redacted] diameter, [redacted] thick and debossed "30/2" and "4833G". The 30+4 tablet is convex-faced, [redacted] diameter, [redacted] thick and debossed "30/4" and "4833G". [redacted] The market package is 30 or 90 tablets in a [redacted] bottle with desiccant. The physician sample is 7 tablets in an aluminum/aluminum push-thru blister package.

This product is intended to be a once-daily dose replacement for two currently approved single-entity drug products. Drug development was based on obtaining a tablet with drug release properties equivalent to Takeda's Actos® (NDA 21-073 for 15mg, 30mg and 45mg Pioglitazone HCl immediate release tablets) and Aventis' Amaryl® (NDA 210-496 for 1mg, 2mg and 4mg Glimepiride tablets).

The formulation and each step of the manufacturing process were investigated with respect to stability, dissolution profiles and manufacturability. [redacted] Tablets were found to be moisture sensitive, thus humidity in the manufacturing area was controlled, appropriate packaging systems were selected, and by a test for moisture content was included at tablet release and in the stability protocols.

Tablets will be manufactured and controlled at Takeda Pharmaceutical Company, Ltd (Osaka, Japan) then [redacted]

Manufacturing is by a multi-step process [redacted]

Time limits are established for [redacted] and justified with stability studies. No [redacted] or [redacted] procedures are proposed. Detailed manufacturing instructions, process parameters and in-process controls are provided along with executed batch records for the [redacted] lots of each proposed tablet strength used to support the application.

All formulation excipients are USP/NF materials which meet monograph requirements. No excipient is a novel material or of human origin. BSE/TSE issues are adequately addressed for excipients which may be of animal origin.

The product release specifications address identity, uniformity, strength, purity and release for each drug substance, and moisture content by loss on drying. Analytical methods are described in detail and validated as

appropriate. Criteria are justified based on batch analysis and stability data obtained on the NDA lots. Impurities observed in the tables are identified by chemical name, molecular structure and mechanism of formation. The analytical methods are shown to quantitate these compounds. The reference standards are those established for drug substance analysis.

The market package is a 90cc [redacted] bottle, [redacted] desiccant, [redacted] and [redacted] child resistant closure. The physician sample package is composed of an aluminum laminate blister film and a push-thru aluminum laminate lidding film. The bulk tablet shipping container is a [redacted] All packaging components are described in detail and qualified for safety, moisture protection and light protection. The component acceptance specifications include tests for identity and dimensions. The market package and shipping container meet the requirements for a tight container and the blister package is a class A unit dose package per USP <671>. The desiccant is intended to control relative humidity in the market package to within a defined limit.

A detailed description of the post approval stability protocol is provided along with the protocol for the NDA stability studies on [redacted] lots of each tablet strength prepared using [redacted] drug substance lots. Stability studies included unprotected tablets under light, heat and humidity stress conditions; and tablets in their market package, physician sample package and shipping container stored at ICH room temperature and accelerated conditions for long periods. Tablets were found to be sensitive to moisture and extended heat exposure. The submitted study data, taken with the stability history of Actos® and Amaryl® tablets, are sufficient to support an initial expiry period of 24 months with storage at USP controlled room temperature and protection from humidity and moisture. The applicant also proposes to extend the expiry period to [redacted] based on additional data from the NDA studies.

CMC information in the draft package insert, patient information leaflet, bottle labels, and labels for the blister, backing, carton and carton display is adequate and complete. The label storage statement is supported by the stability studies.

The applicant has requested a categorical exclusion under 21 CFR 25.3(a) based on the absence of increased drug substance use since the combination tablet is intended to replace two existing single-entity tablets.

DRUG SUBSTANCE – Pioglitazone HCl

Takeda's NDA 21-073 (Actos® 15mg, 30mg, 45mg tablets) is referenced for all CMC information. The applicant has summarized information regarding nomenclature, general properties, manufacturing processes and in-process controls, manufacturing and control sites, acceptance specifications, reference standards, batch analysis data; bulk shipping and storage containers, and the stability studies.

[redacted]

The release specification addresses identity, assay, organic impurities, inorganic impurities, residual solvents, moisture content, and particle size distribution. Analytical methods and their validation studies are summarized. The criteria are justified by batch analysis data on [redacted] commercial lots used to prepare the NDA tablet lots and historical observation. The reference standard, a [redacted] commercial lot, is identified and purity data is provided.

The bulk shipping and storage container is an [redacted]

Stability studies on [redacted] commercial lots in their storage container stored at ICH controlled room temperature and accelerated conditions are summarized and show the material to be stable for [redacted] at USP controlled room temperature.

DRUG SUBSTANCE – Glimepiride

[redacted] ype II DMF [redacted] is referenced for all CMC information. The applicant has summarized information regarding nomenclature, general properties, manufacturing sites, acceptance specifications, reference standards, batch analysis data, bulk storage and shipping containers, and the stability studies.

Drug substance is manufactured and controlled at one site [redacted]

The acceptance specification addresses identity, assay, organic impurities, inorganic impurities, residual solvents, moisture content, particle size distribution and polymorph identity. Analytical methods and their validation studies are summarized. The criteria are justified by the USP monograph, by batch analysis data on [redacted]

commercial lots used to prepare the NDA tablet lots, and by historical observation. The reference standard, a re-purified commercial lot, is identified and purity data is provided.

The bulk storage and shipping container is [redacted]

Stability studies on [redacted] commercial lots in their storage container stored at ICH controlled room temperature and accelerated conditions are summarized and show the material to be stable for [redacted] are USP controlled room temperature.

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

[redacted] is indicated as an adjunct to diet and exercise as a once-daily fixed combination therapy to improve glycemic control in patients with type 2 diabetes who are already being treated with a combination of thiazolidinedione (Pioglitazone) and sulfonylurea (Glimepiride) or whose diabetes is not adequately controlled with sulfonylurea alone. The proposed drug product is Pioglitazone (as the HCl salt) plus Glimepiride formulated as 30mg Pioglitazone + 2mg Glimepiride [30+2], 30mg Pioglitazone + 4mg Glimepiride [30+4], [redacted] strengths. The tablets are immediate release, white to off-white, round, un-coated and debossed with the tablet strength ["30+2", "30+4", [redacted] and "4833G". Tablets are to be taken with a glass of water with maximum dose of [redacted]

Tablets are to be provided in market package and physician sample configurations. The market packages are 30-count and 90-count plastic bottles with desiccant. The physician sample is a [redacted] Labels and labeling are provided for each configuration. The initial expiry period is 24 months with storage at USP controlled room temperature and protection from moisture and humidity.

C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is recommended for APPROVAL in that all relevant CMC issues have been satisfactorily addressed.

III. ADMINISTRATIVE

A. REVIEWER'S SIGNATURE

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William M. Adams, CMC Reviewer for ONDQA

B. ENDORSEMENT BLOCK

M.Adams/CMC Reviewer for ONDQA
S.Moore/PAL for ONDQA
J.Weber/PM for DMEP
S.Goldie/PM for ONDQA

C. CC BLOCK

Chi-wan Chen/ONDQA/dir DPME I
B.Fraser/ONDQA/DPME I/chief Branch II

81 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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
3/20/2006 08:06:41 AM
CHEMIST

Blair Fraser
3/20/2006 08:42:51 AM
CHEMIST

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