

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203414Orig1s000**

**CHEMISTRY REVIEW(S)**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 22426/000	<b>Sponsor:</b>	TAKEDA GLOBAL
<b>Org. Code:</b>	510		1 TAKEDA PKY
<b>Priority:</b>	14S		DEERFIELD, IL 600152235
<b>Stamp Date:</b>	22-SEP-2008	<b>Brand Name:</b>	Oseni (alogliptin and pioglitazone) Tabl
<b>PDUFA Date:</b>	27-JAN-2013	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	28-NOV-2012	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	

001: TABLET; ALOGLIPTIN; 25MG  
001: TABLET; PIOGLITAZONE; 15MG  
002: TABLET; ALOGLIPTIN; 25MG  
002: TABLET; PIOGLITAZONE; 30MG  
003: TABLET; ALOGLIPTIN; 25MG  
003: TABLET; PIOGLITAZONE; 45MG  
004: TABLET; ALOGLIPTIN; 12.5MG  
004: TABLET; PIOGLITAZONE; 15MG  
005: TABLET; ALOGLIPTIN; 12.5MG  
005: TABLET; PIOGLITAZONE; 30MG  
006: TABLET; ALOGLIPTIN; 12.5MG  
006: TABLET; PIOGLITAZONE; 45MG

<b>FDA Contacts:</b>	K. SHARMA	<b>Project Manager</b>	3017961270
	ID = 144440	<b>Review Chemist</b>	
	S. TRAN	<b>Team Leader</b>	3017961764

<b>Overall Recommendation:</b>	ACCEPTABLE	on 22-JAN-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 08-JAN-2013	by EES_PROD		
	PENDING	on 13-SEP-2012	by EES_PROD		
	PENDING	on 02-AUG-2012	by EES_PROD		
	ACCEPTABLE	on 26-AUG-2011	by EES_PROD		
	PENDING	on 25-JUL-2011	by EES_PROD		
	PENDING	on 12-MAY-2011	by EES_PROD		
	WITHHOLD	on 10-MAR-2011	by EES_PROD		
	WITHHOLD	on 11-FEB-2011	by EES_PROD		
	WITHHOLD	on 11-FEB-2011	by EES_PROD		
	WITHHOLD	on 15-JUL-2009	by EES_PROD		

CONFIDENTIAL DATA

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:  
Responsibilities: FINISHED DOSAGE STABILITY TESTER  
Profile: CONTROL TESTING LABORATORY OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 02-AUG-2012  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE MANUFACTURER  
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-JAN-2013  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:  
Responsibilities: FINISHED DOSAGE STABILITY TESTER  
Profile: CONTROL TESTING LABORATORY OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 02-AUG-2012  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE MANUFACTURER  
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 02-AUG-2012  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:  
Responsibilities: FINISHED DOSAGE PACKAGER  
Profile: TABLETS, PROMPT RELEASE OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-AUG-2012  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:  
Responsibilities: FINISHED DOSAGE PACKAGER  
Profile: TABLETS, PROMPT RELEASE OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-AUG-2012  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

COMMITMENT REPORT

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
**DMF No:** (b) (4) **AADA:**  
**Responsibilities:** DRUG SUBSTANCE STABILITY TESTER  
**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 06-AUG-2012  
**Decision:** ACCEPTABLE  
**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: 9610307 FEI: 3004664162  
TAKEDA PHARMACEUTICAL COMPANY LIMITED  
4720 TAKEDA MITSUI  
HIKARI, YAMAGUCHI, JAPAN  
**DMF No:** **AADA:**  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 31-AUG-2012  
**Decision:** ACCEPTABLE  
**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: 9610992 FEI: 3002808311  
TAKEDA PHARMACEUTICAL COMPANY LIMITED  
17-85 JUSO-HONMACHI 2-CHOME  
OSAKA, JAPAN  
**DMF No:** **AADA:**  
**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 08-JAN-2013  
**Decision:** ACCEPTABLE  
**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
**DMF No:** **AADA:**  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
INTERMEDIATE MANUFACTURER  
**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE  
**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 02-AUG-2012  
**Decision:** ACCEPTABLE  
**Reason:** BASED ON PROFILE

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/s/  
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MUTHUKUMAR RAMASWAMY  
01/22/2013

DANAE D CHRISTODOULOU  
01/22/2013

## Memorandum to NDA 203414 File

From: Sheldon Markofsky (Chemistry Reviewer)

Date: December 21, 2012

Subject:

Office of Compliance **Acceptable** Recommendation for the Facilities of NDA 203414

The Office of Compliance has determined that the relevant facilities employed for the manufacture and testing of the drug substances and the drug product (Alogliptin and Metformin Hydrochloride Tablets) are **Acceptable**. Therefore, from both a Chemistry and Office of Compliance point of view, this NDA (2034141) can be approved.

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/s/  
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SHELDON B MARKOFSKY  
12/21/2012

**Memorandum to NDA 203414 File**

From: Sheldon Markofsky (Chemistry Reviewer)

Date: 9-12-12

Subject: Updated stability data for Kazano (alogliptin/metformin HCl tablets)

New data from 24 months of long-term testing under conditions of 25°C/60%RH for all packaging configurations of alogliptin/metformin HCl tablets, were provided in an amendment dated 8-28-12. The additional information shows that the tablets remained within their approved specification at the 24 month time point. The new data supports the 36 month expiry that was previously approved for Kazano.

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/s/  
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SHELDON B MARKOFSKY  
09/12/2012

ALI H AL HAKIM  
09/12/2012

**Memorandum to NDA 203414 File**

From: Sheldon Markofsky (Chemistry Reviewer)

Subject: Updated Specification for alogliptin/metformin HCl tablets

On the basis of an agreement between Takeda Global Research & Development Center, Inc. and the ONDQA/Biopharm review team, the applicant agreed to change the specification for the dissolution of alogliptin/metformin HCl tablets from  $Q = \text{[REDACTED]}^{(b)(4)}$  in 15 min to  $Q = \text{[REDACTED]}^{(b)(4)}$  in 15 min.

(See also the ONDQA Biopharmaceutics Review Addendum, dated 8-6-12.

The revised specification for the alogliptin/metformin HCl tablets is shown on the following page.

## Drug Product Specifications

Test item	Acceptance criteria	Testing Requirement	Analytical procedure
(b) (4)			
<b>Identification</b>			
A. HPLC Retention Time		Release	SYR-322MET-12179
B. Ultraviolet Spectrum		Release	SYR-322MET-12180
Alogliptin			
Metformin hydrochloride		Release	
<b>Disintegration*</b>		Release	USP <701>
<b>Dissolution (%)</b>			SYR-322MET-12184
Alogliptin		Stability	
Metformin hydrochloride		Stability	
<b>Related Substances</b>			
Alogliptin		Release / Stability	SYR-322MET-12181
Total			
Any individual			
Metformin hydrochloride		Release / Stability	SYR-322MET-12182
Total	(b) (4)		
Others (Individual)			
<b>Content Uniformity</b>			SYR-322MET-12183
Alogliptin		Release	
Metformin hydrochloride		Release	
<b>Assay (%)</b>			SYR-322MET-12185
Alogliptin		Release / Stability	
Metformin hydrochloride		Release / Stability	
(b) (4)			

### Appearance specification for 12.5/500 mg tablets

Test item	Acceptance criteria	Testing Requirement	Analytical procedure
Appearance	Pale yellow oblong film-coated tablets with "12.5/500" debossed on one side and "322M" debossed on the other side	Release / Stability	SYR-322MET-12178

### Appearance specification for 12.5/1000 mg tablets

Test item	Acceptance criteria	Testing Requirement	Analytical procedure
Appearance	Pale yellow oblong film-coated tablets with "12.5/1000" debossed on one side and "322M" debossed on the other side	Release / Stability	SYR-322MET-12178

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/s/  
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SHELDON B MARKOFSKY  
08/07/2012

ALI H AL HAKIM  
08/07/2012



**CHEMISTRY REVIEW**

**NDA 203414**

**Kazano  
(Alogliptin and Metformin Hydrochloride) Tablets**

**Takeda Global Research & Development Center, Inc.**

**Sheldon Markofsky, Ph.D.**  
and  
**Muthukumar Ramaswamy, Ph.D.**  
(For the QbD aspects of this NDA)

for

**Division of Metabolism and Endocrine Products (HFD-510)**

and

**Office of New Drug Quality Assessment III Branch VII**

File: 203414g



**CHEMISTRY REVIEW**

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## CHEMISTRY REVIEW

# Chemistry Review Data Sheet

1. NDA 203-414
2. REVIEW #: 1
3. REVIEW DATE: 7-17-12
4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	22-Dec-2011
Initial Quality/ CMC Assessment	10-Jan-2012
Information Request	07-May-2012
Information Request	29-June-2012 (Communicated by E-Mail)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	22-Dec-2011
Amendment <sup>a</sup>	03-April-2012
Amendment <sup>b</sup>	24-May-2012
Amendment <sup>c</sup>	12-June-2012
Amendment <sup>d</sup>	09-July-2012

- a) The 4-3-12 amendment provides additional stability data for the drug product.  
b) The 5-24-12-amendment provides responses to our 5-7-12 Information Request  
c) The 6-12-12 amendment provides documentation to support the 5-24-12-amendment and up-dates the NDA.  
d) The 7-9-12 amendment provides a response to our 6-29-12 Information Request.

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Global Research & Development  
Center, Inc.

Address: One Takeda Parkway  
Deerfield, IL 60015-2235

Representative: Diane Barnes-Glait, Manager, Regulatory  
Strategy

Telephone: (224) 554-2760

## CHEMISTRY REVIEW

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kazano.  
 b) Non-Proprietary Name: Alogliptin and Metformin Hydrochloride Tablets  
 c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: Type 1 NME and Type 4 New Combination
  - Submission Priority: S

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

[The reference listed drug is Glucophage (metformin HCl tablets), NDA 20-357)

### 10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus

### 11. DOSAGE FORM: Tablets

### 12. STRENGTH/POTENCY:

12.5/500 and 12.5/1000 mg (alogliptin/metformin HCl)

### 13. ROUTE OF ADMINISTRATION: Oral

### 14. Rx/OTC DISPENSED: Rx OTC

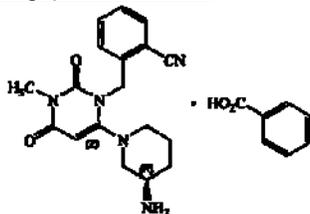
### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

#### Alogliptin Benzoate



$C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$   
 461.51 g/mol

## CHEMISTRY REVIEW

Chemical names:

**INN:** Alogliptin

**USAN:** Alogliptin Benzoate

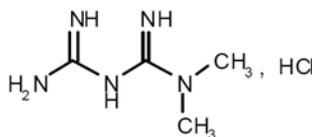
(2-{{6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl}benzotrile monobenzoate

2-[[6-[(3R)-3-Amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2H)-pyrimidinyl)methyl]benzotrile monobenzoate

CAS Registry Numbers: 850649-62-6 (benzoate) and 850649-61-5 (free base)

Company Code: SYR-322

### Metformin HCl



$C_4H_{11}N_5 \cdot HCl$

165.62 g/mol

Chemical names:

Metformin Hydrochloride (INN and USAN names)

N,N-Dimethylimidodicarbonimidic diamide hydrochloride

N,N-Dimethylbiguanide hydrochloride

CAS Registry Number: 115-70-4

Deleted: ¶



**CHEMISTRY REVIEW**

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sub>1</sub>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	2-10-11	Reviewed by Olen Stephens

**Chemistry Review Data Sheet**

<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	101,268	Alogliptin/Metformin HCl Tablets



## CHEMISTRY REVIEW

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	5-10-12	Office of Compliance
Pharm/Tox	Acceptable	7-23-12	David Carlson
Methods Validation	Acceptable	5-7-12	S. B. Markofsky
EA	Acceptable	5-7-12	S. B. Markofsky
Microbiology	N/A		
ONDQA Dissolution/ Disintegration Review	Pending		Houda Mahayni

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

## CHEMISTRY REVIEW

### The Executive Summary

# The Chemistry Review for NDA 203-414

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved. However, the ONDQA/Biopharm Review has not been completed. Thus, the CMC recommendation for approval does not reflect any possible ONDQA/Biopharm concerns.

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### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

None

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## II. Summary of Chemistry Assessments

### A. Description of the Drug Product and Drug Substances

#### 1) Drug Product

The drug product (Kazano) consists of alogliptin / metformin hydrochloride immediate – release (film-coated) tablets. The combination of alogliptin, a dipeptidyl peptidase-4 inhibitor used to improve glycemic control, and metformin hydrochloride, an antihyperglycemic agent, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both alogliptin and metformin are appropriate. Alogliptin and Metformin Hydrochloride immediate –release (film-coated) tablets are proposed to be marketed in 12.5 mg/500 mg, and 12.5 mg/1000 mg strengths. The 12.5 mg/500 mg tablets are:

Pale yellow, oblong (b) (4) film-coated tablets with "12.5/500" debossed on one side and "322M" debossed on the other side

The 12.5 mg/1000 mg tablets are:

Pale yellow, oblong (b) (4) film-coated tablets with "12.5/1000" debossed on one side

**CHEMISTRY REVIEW**

and "322M" debossed on the other side

Packages of 60, 180, or 500 tablets will be marketed in high density polyethylene bottles (HDPE) (b) (4) and physician samples will be available in (b) (4) blister packaging.

Besides alogliptin and metformin HCL, the drug product contains the following inactive ingredients: mannitol, microcrystalline cellulose, povidone, crospovidone, and magnesium stearate. In addition, the tablets are film-coated with hypromellose 2910, talc, titanium dioxide, and ferric oxide yellow. All of the inactive ingredients are compendial.

**2) Drug Substances****Alogliptin Benzoate**

Alogliptin benzoate is manufactured (b) (4) for Takeda. The applicant references their approved NDA 22-271, (Alogliptin Tablets) for the CMC information related to the alogliptin benzoate drug substance. This information is captured in Chemistry Reviews 1 and 2 of NDA 22-271, and NDA 22-271 was recommended for approval from a chemistry point of view.

Alogliptin benzoate is a white to off-white, crystalline powder, containing one asymmetric carbon with a stereochemical configuration of R. It is soluble in dimethyl sulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate (b) (4)

(b) (4) Takeda classifies this drug substance as a Class I compound according to the Biopharmaceutical Classification System (BCS) because of its high solubility and high permeability. Based on the Chemistry reviews of NDA 22-271, this drug substance (alogliptin benzoate) is adequate to support this NDA (203-414).

**Metformin HCL**

Metformin hydrochloride (USP) is manufactured (b) (4) Takeda referenced DMF (b) (4) for the CMC information related to the metformin HCl drug substance, and based on the chemistry reviews of this DMF, this drug substance (metformin HCl) is adequate to support this NDA (203-414).

Takeda specification and testing procedures also comply with the USP monograph for metformin HCl.



## CHEMISTRY REVIEW

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

The individualized starting dose of the alogliptin / metformin hydrochloride tablets should be based on the patient's current regimen and be given twice daily with food, with dose escalation, as appropriate. The maximum recommended dose is 25 mg alogliptin/2000 mg metformin hydrochloride (i.e. two tablets of the highest strength). The stability studies support an expiration-dating period of 36 months for both strengths of the tablets when stored at room temperature [25°C (77°F)], with excursions permitted between 59 °F to 86°F (15°C to 30°C) packaged in all of the proposed commercial container closure systems. Consequently, a 36 month expiry is granted.

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

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, on the following basis:

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, on the following basis:

- Adequate information was provided in the NDA for the synthesis, purification and controls of the drug substances
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product was provided. However an issue related to the substitution of an in-process disintegration test in place of a dissolution specification for the release of the alogliptin/metformin HCl tablets needs to be resolved by the ONDQA/Biopharm Review Team.
- Adequate stability package to support the recommended expiry period of the drug product
- An acceptable Establishment Report for the relevant manufacturing and testing facilities.

Since the ONDQA/Biopharm Review has not been completed, the CMC recommendation for approval does not reflect any possible ONDQA/Biopharm concerns.

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]



## CHEMISTRY REVIEW

### III. Administrative

#### A. Reviewer's Signatures

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)  
Muthukumar Ramaswamy, Ph.D. (Chemistry Reviewer)

#### B. Endorsement Block (OGD only)

N/A

#### C. CC Block (OGD only)

N/A

### Chemistry Assessment

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/s/  
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SHELDON B MARKOFSKY  
07/26/2012

ERIC P DUFFY  
07/26/2012

**DATE:** March 26, 2012

**TO:** SYR-322MET (Alogliptin/Metformin FDC) Review Team (NDA-203414)

**FROM:** Muthukumar Ramaswamy, Ph.D. (Muthukumar.Ramaswamy@fda.hhs.gov, 301-796-1676) on behalf of CMC Review Team

**THROUGH:** Ali Al Hakim, Ph.D. and Eric Duffy, Ph.D.

**SUBJECT:** Product Quality and Manufacturing Memo for NDA 203414

The purpose of this memo is to outline the manufacturing process and control strategy for alogliptin/metformin fixed dose combination (FDC) tablets proposed in the NDA 203414. This memo is not intended to be used as inspectional instructions.

Takeda Global Research and Development Center has proposed 12.5 mg+ 1000 mg and 12.5 mg+ 500 mg SYR-322MET (Alogliptin/ Metformin FDC) tablets for the treatment of Type 2 Diabetes. In addition to alogliptin and metformin, the tablets contain mannitol (b) (4), microcrystalline cellulose (b) (4), povidone (b) (4), crospovidone (b) (4), magnesium stearate (b) (4), hypromellose 2910 (b) (4), talc (b) (4), titanium dioxide (b) (4), ferric oxide (b) (4) yellow (b) (4)

The proposed product will be packaged in (b) (4) blisters and in white opaque high density polyethylene (HDPE) bottles (b) (4)

Takeda plans to manufacture the proposed product at their manufacturing site located at their Osaka plant in Japan. The tablets will be packaged (b) (4)

The Firm used a Quality by Design (QbD) approach to develop the proposed drug product manufacturing process (Refer to Attachment 1 for Process Flow and description). (b) (4)

(b) (4)

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/s/  
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KHUSHBOO SHARMA  
03/26/2012

ERIC P DUFFY  
03/29/2012

ONDQA  
IQA (Initial Quality/CMC Assessment)

**Division of Metabolism and Endocrinology Products**

**NDA: 203414**

**Applicant: Takeda Inc.**

**Stamp Date: 22-NOV-2011**

**PDUFA Date: 22-SEP-2012**

**Proposed Proprietary Name:** (b) (4)

**Established Name:** Alogliptin (free base)/metformin hydrochloride

**Dosage form and strength:** Tablet, 12.5/500 and 12.5/1000 mg/mg

**Route of Administration:** Oral

**Indications:** Treatment of type 2 diabetes.

**CMC Lead:** Su (Suong) Tran, ONDQA

**ONDQA Fileability: Yes**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>COMMENT</b>
Biopharmaceutics	Review of all dissolution-related information.
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 02-DEC-2011.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Pharm/Tox	<i>May not be applicable. Limits on impurities and degradants are within applicable ICH qualification thresholds.</i>

This is an electronic NDA, filed as a 505(b)(2) application, relying Glucophage (metformin hydrochloride). (b) (4)

Reference is made to NDA 22271 (same applicant) for the CMC information on the drug substance alogliptin benzoate. Reference is made to DMF (b) (4) (letter of authorization is provided) for the CMC information on the drug substance metformin hydrochloride.

The product is a fixed dose combination, immediate-release tablet available in the strengths of 12.5/500 and 12.5/1000 mg/mg alogliptin (free base)/metformin hydrochloride. The excipients are mannitol, microcrystalline cellulose, povidone, crospovidone, and magnesium stearate, hypromellose 2910, talc, titanium dioxide, and ferric oxide yellow.

# ONDQA

## IQA (Initial Quality/CMC Assessment)

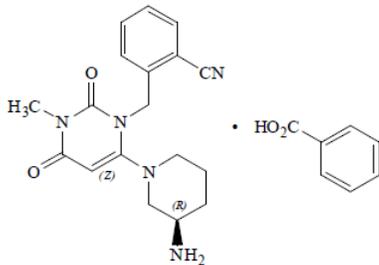
The product will be packaged in bottles (b) (4) and in blisters, and will be stored at room temperature.

Has all information requested during the IND phases and at the pre-NDA meetings been included?  
See the discussion in the review.

### Drug substances

#### **Alogliptin**

Alogliptin is a highly potent, highly selective, orally bioavailable inhibitor of the enzymatic activity of dipeptidyl peptidase-4 (DPP-4). Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3*R*)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)benzotrile monobenzoate. It has a molecular formula of  $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$  and a molecular weight of 461.51 daltons; the structural formula is:

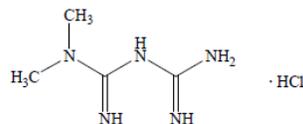


Alogliptin benzoate is a white to off-white, crystalline powder, containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate.

Reference is made to NDA 22271 (same applicant) for the CMC information on the drug substance alogliptin benzoate.

#### **Metformin hydrochloride**

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of  $C_4H_{11}N_5 \cdot HCl$  and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Reference is made to DMF (b) (4) (letter of authorization is provided) for the CMC information on the drug substance metformin hydrochloride.

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Drug product:

**Table 1.b** Composition of SYR-322MET Tablets, (b) (4),  
 12.5mg+500mg, and 12.5+1000mg

Component	Reference to Quality Standards	Function	Quantity per Tablet (mg)	
			(b) (4) 12.5mg +500mg	(b) (4) 12.5mg +1000mg
(b) (4)				
Alogliptin benzoate (As the free base)	In-house standard	Active ingredient	17 (12.5)	17 (12.5)
Mannitol	Ph.Eur., USP	(b) (4)		
Microcrystalline cellulose	Ph.Eur., NF			
Povidone	Ph.Eur., USP			
(b) (4)				
Metformin hydrochloride	Manufacturer's standard (b) (4)	Active ingredient	(b) (4) 500	(b) (4) 1000
(b) (4)				
Crospovidone	Ph.Eur., NF	(b) (4)		
Magnesium stearate	Ph.Eur., NF			
(b) (4)				
<b>Film-Coating</b>			(b) (4)	
(b) (4)				
Hypromellose 2910	Ph.Eur., USP	(b) (4)		
Talc	Ph.Eur., USP			
Titanium dioxide	Ph.Eur., USP			
(b) (4)				
Ferric oxide, yellow	95/45/EC (E172), NF	(b) (4)		
(b) (4)				
<i>Tablet weight</i>			(b) (4)	730 1350
(a) (b) (4)				

(b) Also meets USP.

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SYR-322MET tablets are oblong, (b) (4) film-coated tablets produced in 4 strengths; (b) (4) 12.5mg+500mg and 12.5mg+1000mg of alogliptin and metformin HCl, respectively. All 4 strengths were developed as potential commercial formulations. The 4 strengths are distinguished by size and by film color. A description of the appearance of SYR-322MET tablets is provided below.



12.5mg+500mg: Pale yellow, oblong (b) (4) film-coated tablet with "12.5/500" debossed on one side and "322M" debossed on the other side

12.5mg+1000mg: Pale yellow, oblong (b) (4) film-coated tablet with "12.5/1000" debossed on one side and "322M" debossed on the other side

Figure 1 SYR-322MET Tablet Appearance



- **Formulations.** (b) (4)  
(b) (4)  
(b) (4)  
(b) (4)  
(b) (4)  
(b) (4)
- **Dosage strength.** The dosage strengths are based on the established names of the drug substances, alogliptin and metformin hydrochloride. This is in accordance with the current CDER policy that the dosage strength and established name must match. The tables of composition include both the free-base and salt amounts for alogliptin (benzoate).

6 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

ONDQA  
 IQA (Initial Quality/CMC Assessment)

**PRODUCT QUALITY**  
**FILING REVIEW FOR NDA (ONDQA)**

NDA Number: 203414

Established/Proper Name:  
 Alogliptin/metformin hydrochloride  
 Stamp Date: 22-NOV-2011

Applicant: Takeda

Letter Date: 22-NOV-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

ONDQA  
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9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

ONDQA  
 IQA (Initial Quality/CMC Assessment)

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue: whether data and analysis are adequate to support expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	x		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Not applicable
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

*{See appended electronic signature page}*

Su (Suong) Tran  
 CMC Lead, Office of New Drug Quality Assessment  
*{See appended electronic signature page}*  
 Ali Al Hakim  
 Branch Chief, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Date *{see appended electronic signature page}*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUONG T TRAN  
01/10/2012

ALI H AL HAKIM  
01/10/2012