

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022271Orig1s000**

**CHEMISTRY REVIEW(S)**

# memo

To: File  
From: Ramaswamy, Muthukumar, Ph.D., Office New Drug Quality Assessment, OPS, CDER  
CC: Ali Al Hakim, Ph.D., Office New Drug Quality Assessment, OPS, CDER  
Date: 12/12/2012  
Re: CMC Recommendation for NDA 22271 and 22426 – NESINA® (alogliptin) Tablets and Oseni® (alogliptin/pioglitazone) fixed-dose combination (FDC) tablets

Comments: On July 26 and 27, 2012, Takeda resubmitted NDA 22-271 and NDA 22426 in response to issues identified in Agency's April 2012 Complete Response letter.

On August 27, 2012. Takeda has submitted an amendment to the NDA for adding a drug product manufacturing site and later on 10/23/12, Takeda has withdrawn this request.

Review of the recent CMC reviews in DARRTS for these two NDAs indicated that there are no outstanding CMC issues identified for NDA 22271 and 22426.

*Recommendation: From the CMC perspective, both NDAs 22271 and 22426 are recommended for approval.*

Please note that as of 12/12/12, the Office of Compliance's overall recommendation for GMP inspections is still outstanding. The CMC recommendation does not incorporate any potential facility inspection issues.

*For dosage form description and shelf-life recommendation, please refer to CMC review dated 01/04/12 in DARRTS.*

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MUTHUKUMAR RAMASWAMY  
12/12/2012

ALI H AL HAKIM  
12/12/2012

## Memorandum to NDA 22271 File

From: Muthukumar Ramaswamy, Ph.D. (Chemistry Reviewer)

Date: January 3, 2013

Subject: Office of Compliance **Acceptable** Recommendation for the Facilities Associated With NDA 22271

Drug Product Name/Strength: NESINA® (alogliptin) Tablets/6.25 mg, 12.5 mg, 25 mg

Ref.: Previous CMC review dated 12/12/12 for NDA 22271 in DARRTS.

The Office of Compliance (OC) has determined that the relevant facilities employed for the manufacture and testing of the drug substances and the drug product (Alogliptin Tablets) are **Acceptable**. Therefore, from both CMC perspective and Office of Compliance point of view, this NDA (22271) is recommended for approval.

Attachment: Section of Establishment Evaluation Request Summary Report from OC indicating the Acceptable recommendation.

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

<b>Application:</b>	NDA 22271/000	<b>Sponsor:</b>	TAKEDA GLOBAL
<b>Org. Code:</b>	510		1 TAKEDA PKY
<b>Priority:</b>	1S		DEERFIELD, IL 600152235
<b>Stamp Date:</b>	27-DEC-2007	<b>Brand Name:</b>	ALOGLIPTIN
<b>PDUFA Date:</b>	26-JAN-2013	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	27-NOV-2012	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
			001; TABLET; ALOGLIPTIN; 25MG 002; TABLET; ALOGLIPTIN; 12.5MG 003; TABLET; ALOGLIPTIN; 6.25MG
<b>FDA Contacts:</b>	R. MCKNIGHT	Project Manager	3017961765
	ID = 105115	Review Chemist	
	S. TRAN	Team Leader	3017961764

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**Overall Recommendation:** ACCEPTABLE on 02-JAN-2013 by D. SMITH (HFD-323) 3017965321

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/s/  
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MUTHUKUMAR RAMASWAMY  
01/03/2013

ALI H AL HAKIM  
01/03/2013

**CMC Review of Complete Response  
December 12, 2011**

**NDA 22-271: Alogliptin  
NDA 22-426: Alogliptin – Pioglitazone FDC**

**Sponsor:** Takeda Global Research & Development Center  
Sandra D. Cosner, RPh, Associate Director, Regulatory Affairs  
One Takeda Parkway  
Deerfield, IL 60015-2235  
(224) 554-1957

**Mechanism of action:** DPP-4 inhibitor and DPP-4 inhibitor/TZD  
**Indication:** Type 2 diabetes mellitus

**Receipt Date:** July 25, 2011  
**Class 2 resubmission 6-month Goal Date:** January 25, 2012  
**Extension due to additional clinical data:** April 25, 2012

**CMC Recommendation:** Approve

**CMC Review:**

This submission has been provided in response to FDA's complete response letter, issued June 26, 2009. At that time, there were outstanding CGMP pre-approval inspectional issues and biopharmaceutics dissolution method issues with these Applications. The following table summarized the CMC status of the two resubmissions, noting revised or updated data provided to support these Applications.

22-271 <sup>1</sup>	22-426 <sup>2</sup>	Task	Status	Status date	Comment(s)
X		EES	Acceptable	05-OCT-2011	Based on the EES evaluation, this aspect of the Application is concluded; no further action is indicated at this time.
X		CMC Recommendation	Acceptable	16-JAN-2009	(From last CMC review entered into DARRTS by S. Tran)  -The retest period of the drug substance is (b) (4) at (b) (4). The expiration dating period for the 12.5 mg

<sup>1</sup> No specific CMC non-approval issues were communicated in the CR letter. Current OC recommendation is acceptable in support of this review cycle. No new CMC information was submitted in this CR.

<sup>2</sup> Failure of the PAI was noted in CR letter. Current OC recommendation is acceptable in support of this review cycle. No new CMC information was submitted in this CR.

and 25 mg tablets is three years at 25 °C/60% RH. The expiration dating period for the 6.25 mg tablets is thirty months at 25 °C/60% RH.

-It should be noted that Form 365h for the NDA lists only the dosage strengths of 6.25 mg, 12.5 mg, and 25 mg. **In the Action letter, the applicant should be reminded that the (b)(4) strength was not reviewed as part of the NDA.**

-An "acceptable" recommendation from Compliance was issued on 16-JAN-2009.

X	Drug Product Information	<p>NESINA (alogliptin) Tablets are available as oval, biconvex, film-coated, immediate release tablets of 6.25 mg, 12.5 mg or 25 mg of alogliptin as follows:</p> <p>6.25 mg light pink tablet printed with "TAK ALG-6.25" on one Side, packaged in 30-count and 90- count high-density polyethylene (HDPE) bottles.</p> <p>12.5 mg yellow tablet printed with "TAK ALG-12.5" on one side, packaged in 7-count, 30-count, 90-count and 500- count HDPE bottles and in 7-count (b)(4) foil blisters.</p> <p>25 mg light red tablet, printed with "TAK ALG-25" on one side, packaged in 7-count, 30-count, 90-count and 500- count HDPE bottles and in 7-count (b)(4) foil blisters.</p>
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22-271	22-426	Task	Status	Status date	Comment(s)
	X	EES	Acceptable	26-AUG-2011	Based on the EES evaluation, this aspect of the Application is concluded; no further action is indicated at this time.
	X	CMC	Approvable <sup>3</sup>	14-JUL-	CMC-Biopharmaceutics negotiations are

<sup>3</sup> CMC Biopharmaceutics review entered into DARRTS 02-AUG-2011. PMA will be crafted indicating that; "Takeda will conduct an additional 12 months of dissolution evaluation (post approval) using the current specification of Q=(b)(4) in 30 minutes. At the end of the one year period, if the additional data

	Recommendation	2011	ongoing concerning responses to a CMC PMA to evaluate paddle speed change in the drug product dissolution method. A new dissolution method has been submitted by the Applicant.
X	Drug Product Information		<p>The drug product is (b) (4) film-coated, immediate-release tablets. The proposed dosage forms and strengths (free base alogliptin/ free base pioglitazone) are:</p> <p>25 mg/15 mg tablets are yellow, round, biconvex, film-coated tablets, with both “A/P” and “25/15” printed on one side.</p> <p>25 mg/30 mg tablets are peach, round, biconvex, film-coated tablets, with both “A/P” and “25/30” printed on one side.</p> <p>25 mg/45 mg tablets are red, round, biconvex, film-coated tablets, with both “A/P” and “25/45” printed on one side.</p> <p>12.5 mg/15 mg tablets are pale yellow, round, biconvex, film-coated tablets, with both “A/P” and “12.5/15” printed on one side.</p> <p>12.5 mg/30 mg tablets are pale peach, round, biconvex, film-coated tablets, with both “A/P” and “12.5/30” printed on one side.</p> <p>12.5 mg/45 mg tablets are pale red, round, biconvex, film-coated tablets, with both “A/P” and “12.5/45” printed on one side.</p> <p>Tablets of the drug product are provided in both physician samples and commercial package configurations.</p>

clearly support the specification change, Takeda would commit to implementing and reporting the revised (b) (4) specification from Q=(b) (4) in 30 minutes to Q=(b) (4) in 15 minutes in the first Annual Report. However, if the additional data do not support the change in the dissolution specification to Q=(b) (4) in 15 minutes, Takeda would provide, for the Agency’s review, the data and the justification for maintaining the specification at Q=(b) (4) at 30 minutes.”

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The physician samples are provided in 7- (b)(4) count HDPE bottles and 7-count blister packs. The commercial marketed packages consist of 30-, 90-, and 500-count HDPE bottles.

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**Outstanding Biopharmaceutics Dissolution Issue:**

On December 6, 2011, the following biopharmaceutics comment was sent to the Applicant:

The sponsor's revised dissolution method using Apparatus 2 with PEAK vessels at 50 rpm is acceptable. However, based on the dissolution profiles submitted by the sponsor using Apparatus 2 with PEAK vessels at 50 rpm, the Agency recommends the following dissolution condition for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone) with the following dissolution specifications:

*Medium: 900 mL of pH 2.2 Sørensen buffer (without deaeration)*  
*Apparatus: 2 with PEAK vessels*  
*Paddle rotation speed: 50 rpm*  
*Alogliptin:  $Q =$  (b)(4) of the labeled amount dissolved in 15 minutes.*  
*Pioglitazone:  $Q =$  (b)(4) of the labeled amount dissolved in 30 minutes for one year after product approval.*

Takeda committed to further evaluate product release and stability data for pioglitazone dissolution from SYR-322-4833 tablets at both 15 and 30 minutes for one year after product approval, while maintaining the current specification of  $Q =$  (b)(4) in 30 minutes.

- a. In the course of this one year evaluation period post-approval, Takeda would collect release data for multiple commercial lots and stability data at testing intervals up to 24 months.
- b. At the end of the one year period, if the additional data clearly support the specification change, Takeda would commit to implementing and reporting the revised (b)(4) specification from  $Q =$  (b)(4) in 30 minutes to  $Q =$  (b)(4) in 15 minutes.
- c. However, if the additional data do not support the change in the dissolution specification to  $Q =$  (b)(4) in 15 minutes, Takeda would provide, for the Agency's review, the data and the justification for maintaining the specification at  $Q =$  (b)(4) at 30 minutes.

On December 22, 2011, the biopharmaceutics reviewer recommended approval of the dissolution testing for the combination tablet under NDA 22-426, noting the following:

Based upon Takeda Global Research & Development's (TGRD) amendment to NDA 22-426 (SDN-031, dated July 27, 2011), and FDA's follow-up emails dated August 9, 2011 and December 7, 2011, via this amendment (SDN-042 dated December 13, 2011) Takeda officially committed to the following:

1. To further evaluate the pioglitazone dissolution specification (using the new 50 rpm/PEAK vessel dissolution method) by collecting product release and stability data for pioglitazone dissolution from SYR-322-4833 tablets at both 15 and 30 minutes for one year after product approval, while maintaining the current specification of  $Q = \text{(b) (4)}$  in 30 minutes (as the interim pioglitazone dissolution specification).
2. In the course of this one year evaluation period post-approval, Takeda will collect release data for multiple commercial lots and stability data at testing intervals up to 24 months.
3. At the end of the one year period, if the additional dissolution data clearly support the pioglitazone dissolution specification change  $\text{(b) (4)}$ , Takeda will commit to implementing the revised  $\text{(b) (4)}$  specification of  $Q = \text{(b) (4)}$  in 15 minutes (from  $Q = \text{(b) (4)}$  in 30 minutes). This change will be reported in a supplement to the NDA.
4. However, if the additional data do not support the  $\text{(b) (4)}$  change in the pioglitazone dissolution specification to  $Q = \text{(b) (4)}$  in 15 minutes, Takeda will provide, in a supplement to the NDA, the additional dissolution data and the justification for maintaining the specification at  $Q = \text{(b) (4)}$  at 30 minutes as the final dissolution acceptance criteria for pioglitazone.

Overall, all outstanding CMC issues have been resolved; the final CMC recommendation is approve.

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JOHN C HILL  
01/04/2012

ALI H AL HAKIM  
01/04/2012

**Date:** 24-MAR-2009  
**From:** Su (Suong) Tran, Pharmaceutical Assessment Lead, Branch II/DPA I/ONDQA  
**To:** NDA 22-271 alogliptin tablets  
**Through:** Ali Al Hakim, Branch Chief, Branch II/DPA I/ONDQA  
**Subject:** Chemistry Review #3 – Amendments dated 16-MAR-2009 and 25-MAR-2009

Background:

- The most recent Chemistry Review of this NDA (Chem. Rev. #2, by Chemist Chien Hua Niu) recommended “approvable” on 10-SEP-2008. As indicated in the Chem. Rev. #2, all CMC issues were adequately resolved, but an overall recommendation from the Office of Compliance on the GMP status of manufacturing and testing facilities was still pending. An “acceptable” recommendation from Compliance was issued on 16-JAN-2009.
- An unsolicited amendment was submitted by the Applicant on 16-MAR-2009 for additional stability data for both the drug substance and drug product. This amendment will not affect the action goal date, as previously agreed by FDA on 10-NOV-2008. This Chem. Rev. #3 is the review of this new amendment.

Reviewer’s comments:

- In the previous Chem. Rev. #2, the retest period (b) (4) for the drug substance was granted by FDA. (b) (4)  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]  
[Redacted]
- In the previous Chem. Rev. #2, the expiration dating period (b) (4) for the drug product was granted by FDA. It was based on 12-month 25 °C/60% RH data and 6-month 40 °C/75% RH data for the primary 6.25 mg drug product lots Z641K01, Z641K02, and Z641K03, 12.5 mg product lots Z641601, Z641602, and Z641603, and 25 mg product lots Z641701, Z641Z702, and Z641703. Each lot was packaged in all the packaging systems proposed for marketing. In the 16-MAR-2009 amendment, data at two additional time points, Months 18

and 24 at 25 °C/60% RH, are provided for the same primary lots of the 12.5 mg and 25 mg strengths. The additional data show no negative stability trend compared to the previously reviewed data at the earlier time points. Therefore, the applicant's proposed expiration dating period of three years (b)(4) is acceptable for the 12.5 mg and 25 mg strengths as per ICH Q1E ("Y = up to 2X, but not exceeding X + 12 months"). In addition, the amendment provides data at the additional time point of Month 18 at 25 °C/60% RH for the 6.25 mg primary lots. The additional data show no negative stability trend compared to the previously reviewed data at the earlier time points. The amendment also provides 18-month stability data for this dosage strength packaged in the (b)(4) blister (same blister as for the higher strengths). The same stability profiles were obtained for the blister and bottle systems used to package this lowest dose. Therefore, the applicant's proposed expiration dating period of 30 months (b)(4) is acceptable for the 6.25 mg strength.

- The 16-MAR-2009 amendment includes an updated stability protocol to add the blister packaging system for the 6.25 mg strength, which is acceptable. Information is provided on the alternate test method and validation reports for the microbial limit test in the drug substance and drug product specifications. As indicated in the Chem. Rev. #1, this microbial limit test is performed for information purposes only. Therefore, the updated information in the amendment is acceptable.

**Conclusion: The CMC recommendation for this NDA 22-271 alogliptin tablets is APPROVAL.**

- **The retest period of the drug substance is (b)(4) at (b)(4). The expiration dating period for the 12.5 mg and 25 mg tablets is three years at 25 °C/60% RH. The expiration dating period for the 6.25 mg tablets is thirty months at 25 °C/60% RH.**
- It should be noted that Form 365h for the NDA lists only the dosage strengths of 6.25 mg, 12.5 mg, and 25 mg. **In the Action letter, the applicant should be reminded that the (b)(4) strength was not reviewed as part of the NDA.**
- An "acceptable" recommendation from Compliance was issued on 16-JAN-2009.

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Suong Tran  
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Ali Al-Hakim  
3/30/2009 11:00:40 AM  
CHEMIST

**NESINA®  
(alogliptin)  
Tablets**

**NDA 22-271**

**Division Director Review  
Chemistry, Manufacturing, and Controls**

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

**Indication:** Treatment of Type 2 Diabetes

**Presentation:** NESINA® (alogliptin) Tablets are film-coated, oval, immediate release tablets of 6.25 mg (light pink, oval), 12.5 mg (yellow, oval) or 25 mg (red) strength supplied in HDPE bottles and foil blisters.

**EER Status:** **Pending**

**Consults:** EA – Categorical exclusion granted under 21 CFR §25.31(b)  
Methods Validation – Revalidation by Agency will not be requested.

**Original Submission:** 27-DEC-2007

**Post-Approval Agreements:** None

**Remarks:**

This application was chosen by the Division of Metabolism and Endocrinology Products to serve as the pilot for the *Good Review Management Principles and Practices (GRMPs) for PDUFA Products (April 2005)*.

**Drug Substance:**

The drug substance, alogliptin benzoate, is a highly selective and potent inhibitor of dipeptidyl peptidase-4 (DPP4). Inhibitors of this enzyme are a new class of antihyperglycemic agents for type 2 diabetes mellitus, which prolong the activity of incretin hormones and thereby enhance insulin secretion and suppress glucagon secretion in a glucose-dependent manner. It is a small, synthetic, new molecular entity (NME) with an empirical formula of  $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$  and a molecular weight of 461.51 (free base: 339.39). Known chemically as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzotrile monobenzoate. It is white to off-white crystalline powder that melts with decomposition at about 182.5 °C. The drug substance contains one chiral center and has (b) (4)

the R stereochemical configuration. It is sparingly soluble in water (19.2 mg/mL), sparingly soluble in methanol, slightly soluble in ethanol, soluble in dimethyl sulfoxide, and highly soluble in aqueous solutions at 37°C. The pKa of the protonated base is 8.5.

(b) (4)

The manufacture of alogliptin benzoate is

(b) (4)

The structure of alogliptin benzoate was elucidated using single crystal X-ray Diffraction (XRD), elemental analysis, <sup>1</sup>H and <sup>13</sup>C Nuclear Magnetic Resonance spectroscopy (NMR), electron ionization Mass Spectrometry (EI-MS), InfraRed absorption spectroscopy (IR), and UltraViolet spectroscopy (UV).

The proposed release specification for alogliptin benzoate includes: appearance, identification by IR and UV, identification by Reverse Phase High Performance Liquid Chromatography (RP-HPLC), (b) (4) HPLC, related substances by RP-HPLC, water by Karl Fischer, residue on ignition, assay by RP-HPLC, heavy metals, residual solvents by Gas Chromatography (GC), particle size by light scattering. The reference standard (b) (4)

(b) (4) has been thoroughly characterized to meet more stringent specification. The impurities and degradation products have been investigated. Impurity reference standards have likewise been (b) (4) characterized.

Adequate stability data were provided to support a (b) (4) retest date for the bulk drug substance,

(b) (4)

**Conclusion:** Drug substance is acceptable.

### **Drug Product:**

NESINA® (alogliptin) Tablets are available as oval, biconvex, film-coated, immediate release tablets of 6.25 mg, 12.5 mg or 25 mg of alogliptin as follows:

6.25 mg light pink tablet printed with "TAK ALG-6.25" on one Side, packaged in 30-count and 90- count high-density polyethylene (HDPE) bottles.

12.5 mg yellow tablet printed with "TAK ALG-12.5" on one side, packaged in 7-count, 30-count, 90- count and 500- count HDPE bottles and in 7-count (b) (4) foil blisters.

25 mg light red tablet, printed with "TAK ALG-25" on one side, packaged in 7-count, 30-count, 90-count and 500-count HDPE bottles and in 7-count (b) (4) foil blisters.

The drug product is manufactured (b) (4)

(b) (4) Adequate information on the drug product manufacture has been provided.

(b) (4)  
6.25 mg strength tablet is alogliptin benzoate (8.5 mg)  
12.5 mg strength tablet is alogliptin benzoate (17 mg)  
the 25 mg strength tablet is alogliptin benzoate (34 mg)

(b) (4)  
The  
(b) (4); the  
(b) (4); and  
(b) (4)  
(b) (4)

(b) (4) The colored film coating, containing hypromellose, titanium dioxide, triacetin, ferric oxide yellow, and ferric oxide red (b) (4)

Specification of the drug product includes: appearance, identification by RP-HPLC, identification by UV, assay by RP-HPLC, impurities and related substances by RP-HPLC, content uniformity by RP-HPLC, percent dissolution (b) (4) The alogliptin benzoate reference standard for drug product is (b) (4) (b) (4) The proposed regulatory methods are either compendial or were developed and validated for their intended purpose.

A (b) (4) expiration date has been assigned to the product based on the provided stability data when stored at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F).

**Conclusion:** Drug product is acceptable.

**Additional Items:**

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

The applicant agreed to follow the stability of the first three packaged lots of different bulk batches of each strength of product and submit the results to the Annual Report.

The applicant agreed to place at least one commercial production lot of the drug product per year on stability for each strength and package configuration following the approved stability protocol.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product. These methods are routine and will not be submitted to FDA laboratories for validation.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for **Approval**, pending an acceptable recommendation from the Office of Compliance

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

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/s/

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Blair Fraser  
9/10/2008 12:23:36 PM  
CHEMIST

**NDA 22-271**

**NESINA  
(Alogliptin)  
Tablets**

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

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

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# Chemistry Review Data Sheet

1. **NDA 22-271**
2. REVIEW #: 2
3. REVIEW DATE: September 10, 2008
4. REVIEWER: Chien-Hua Niu, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<b>Submission Type</b>	<b>Document Date</b>
Original	27-DEC-2007
Amendment	22-JUL-2008
Amendment	25-AUG-2008
Amendment	29-AUG-2008
Amendment	05-SPT-2008

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NESINA<sup>TM</sup> Tablets
- b) on-Proprietary Name (USAN): Alogliptin
- c) Code Name/# (ONDC only): 850649-62-6 (CAS registry number)
- 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: Inhibitor of the dipeptidyl peptidase-4 (DPP-4)
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 6.25 mg, 12.5 mg, and 25 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:   X   Rx      OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

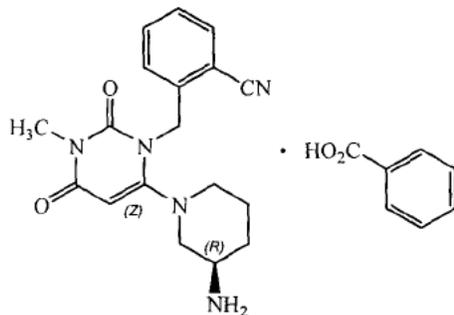
     SPOTS product – Form Completed

  X   Not a SPOTS product

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

Chemical Name: Alogliptin benzoate

Structural Formula:



Molecular Formula: C<sub>18</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub> · C<sub>7</sub>H<sub>6</sub>O<sub>2</sub>

Molecular Weight: 461.51 g/mol (benzoate salt)

339.39 g/mol (free base)

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA	PREVIOUS REVIEW	RECOMMENDATION
(b) (4)	III	(b) (4)	(b) (4)	16-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III		05-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		12-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		05-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		12-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		18-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		16-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		14-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		14-NOV-2007			
	III		18-OCT-2007			
	IV		10-OCT-2007		DMF reviewed by the reviewer	Adequate

\*Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

<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	69,707	Alogliptin used for the treatment of Type 2 diabetes

Chemistry Review Data Sheet

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	Complete		Mei-yu Shen
EES	Pending		Office of Compliance
Pharm/Tox	N/A		David Carlson
Biopharm	N/A		Sang Chung
LNC	N/A		
Methods Validation	Not required at this time		Chien-Hua Niu
DMETS	Pending		
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

Since all chemistry issues have been adequately resolved, the final Chemistry recommendation is still pending the Overall Recommendation from the Office of Compliance for the CGMP status of manufacturing and testing facilities.

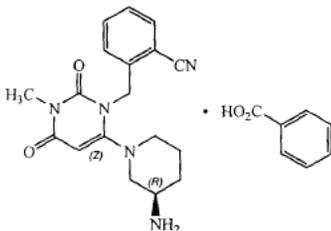
#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

### II. Summary of Chemistry Assessments

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

Alogliptin is a highly potent and highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme that rapidly degrades incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). In patients with type 2 diabetes, levels of GLP-1 are reduced and the action of both GLP-1 and GIP are blunted. This markedly diminished incretin effect contributes to hyperglycemia. DPP-4 inhibition targets the incretin defect by increasing circulating blood levels of endogenous incretins, which increase insulin levels and decrease glucagon levels in a glucose-dependent manner. The increase in insulin levels enhances glucose uptake by tissues, and the decrease in glucagon levels reduces hepatic glucose production leading to improve glycemic controls.

**DRUG SUBSTANCE:** Alogliptin benzoate is designated chemically as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzotrile monobenzoate. The chemical structure and molecular formula for alogliptin benzoate are shown below:



Alogliptin benzoate is a new molecular entity manufactured by (b) (4). The API has one chiral center with stereochemical configuration of R. The manufacturing process for alogliptin benzoate is (b) (4).

## REVIEW NOTE

The structure of alogliptin was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ) spectroscopy, mass spectrometry, and X-ray crystallography. Alogliptin benzoate is a white to off-white crystalline powder, and decomposed with melting at approximately  $182.5^\circ\text{C}$ . It has a molecular weight of 416.51 (benzoate salt). It is highly soluble in DMSO, moderately soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate.

Results from X-ray diffraction studies demonstrate (b) (4)

The proposed release specifications include appearance, identification (IR and UV), heavy metals, (b) (4) assay, water content, assay, related substance, residual solvents, and particle size. The proposed regulatory methods have been validated. The impurities and degradation products have been investigated. Reference standard for API has been developed and characterized.

Based on data from ICH stability studies on 3 lots, alogliptin benzoate is stable (b) (4)

**DRUG PRODUCT:** The proposed drug product is manufactured by Takeda Pharmaceutical Company Ltd (Osaka, Japan). NESINA tablets are available as film-coated immediate release tablets containing 6.25 mg, 12.5 mg or 25 mg of alogliptin as follows:

6.25 mg tablet: light pink, oval, biconvex, film-coated tablet, with "TAK ALG-6.25" printed on one side.

12.5 mg tablet: yellow, oval, biconvex, film-coated tablet, with "TAK ALG-12.5" printed on one side.

25 mg tablet: light red, oval, biconvex, film-coated tablet, with "TAK ALG-25" printed on one side.

NESINA tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate; the tablets are film-coated with hypromellose, titanium dioxide, ferric oxide (red and yellow), and polyethylene glycol, and marked with printing ink (b) (4). All excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail.

NESINA tablets are manufactured (b) (4)

Finally, the film-coated tablets are printed (b) (4) and packed into a suitable container.

The proposed release specifications include appearance, identification (UV and HPLC), assay (HPLC), related substances (HPLC), dissolution, and content uniformity. The proposed regulatory methods have been validated.

## REVIEW NOTE

NASINA tablets (12.5 mg and 25 mg) are packaged in 7-count, 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles. These tablets are also packaged in 7-count (b) (4) foil blister. For 6.26 mg tablets, they are packaged in 30-count and 90-count HDPE bottles.

NESINA tablets packaged in different HDPE bottle configurations or blister package show no significant changes in terms of appearance, assay, related substances, dissolution, (b) (4) and hardness when stored at long term condition (25°C/60% RH) for 12 months and at accelerated conditions (40°C/75% RH). However, the (b) (4) degradation product has the relative retention time (RRT) of (b) (4). Levels for this related substance reached a (b) (4)

The photostability study indicates that NESINA tablets are not light sensitive.

Based on statistical analyses of stability data from samples packaged in HDPE bottles and blisters and stored at 25°C/60% RH for a period of 12 months, an expiration dating period (b) (4) is recommended for NESINA tablets.

The firm agrees to incorporate the requirement for the evaluation of (b) (4) in the stability protocols and testing. Moreover, the firm also proposes to set a specification for the results of this testing of Not More Than (b) (4) (see the 8/29/2008 amendment).

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

Regarding comparability protocol, the FDA recommends that any changes in the manufacturing sites for the drug substance and drug product can be implemented after approval of a post-approval supplemental application for the NDA and a satisfactory CGMP status verified by the Office of Compliance of the FDA. In the 9/5/2008 amendment, the firm agrees to follow the FDA's recommendation.

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

NESINA is an inhibitor of the dipeptide-peptidase-4 (DPP-4) enzyme and is indicate as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (type 2 diabete). The recommended dose of NESINA is 25 mg once daily, as immunotherapy or as combination therapy.

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

The recommendation that this application can be approved from a CMC viewpoint is based on the following: (1) The general procedures for the synthesis of alogliptin benzoate are outlined in the NDA. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Three primary stability batches for each dose strength of the 6.25 mg, 12.5 mg, and 25 mg Alogliptin Tablets have been manufactured by Takeda Pharmaceutical Company Ltd. at Osaka, Japan. All these batches were produced with the drug substance manufactured by (b) (4) and (4) Stability data for the drug

**REVIEW NOTE**

product indicate that no significant changes were observed in terms of appearance, related substances, dissolution, assay, hardness, (b) (4) and microbial limit when stored at 25°C/60% RH for a period of 12 months and at 40°/75% RH for 6 months.

**Pending Issue:** CGMP inspection of the manufacturing sites for the drug product (Takeda Pharmaceutical Company Ltd., Osaka, Japan) has not been completed by the Office of Compliance.

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

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

Chemistry Branch Chief Name/Date: Ali Al Hakim, Ph.D. /ONDQA/DPMA-I/Branch-II

**C. CC Block**

Dr. Su Tran/Dr. Blair Fraser

Project Manager Name/Date: Julie Marchick, OND/HFD-510

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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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Chien-Hua Niu  
9/10/2008 11:10:23 AM  
CHEMIST  
The CMC Review #2

Ali Al-Hakim  
9/10/2008 11:17:19 AM  
CHEMIST

**NDA 22-271**

**NESINA  
(Alogliptin)  
Tablets**

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

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

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# Chemistry Review Data Sheet

1. **NDA 22-271**

2. REVIEW #: 1

3. REVIEW DATE: August 18, 2008

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

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission Type	Document Date
Original	27-DEC-2007
Amendment	22-JUL-2008

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NESINA<sup>TM</sup> Tablets
- b) on-Proprietary Name (USAN): Alogliptin
- c) Code Name/# (ONDC only): 850649-62-6 (CAS registry number)
- 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: Inhibitor of the dipeptidyl peptidase-4 (DPP-4)
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 6.25 mg, 12.5 mg, and 25 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:   X   Rx      OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

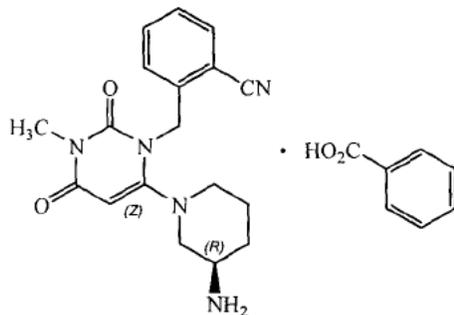
     SPOTS product – Form Completed

  X   Not a SPOTS product

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

Chemical Name: Alogliptin benzoate

Structural Formula:



Molecular Formula: C<sub>18</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub> · C<sub>7</sub>H<sub>6</sub>O<sub>2</sub>  
Molecular Weight: 461.51 g/mol (benzoate salt)  
339.39 g/mol (free base)

Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA	PREVIOUS REVIEW	RECOMMENDATION
(b) (4)	III	(b) (4)	(b) (4)	16-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III		05-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		12-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		05-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		12-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		18-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		16-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		14-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		14-NOV-2007			
	III		18-OCT-2007			
	IV		10-OCT-2007		DMF reviewed by the reviewer	Adequate

\*Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

<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	69,707	Alogliptin used for the treatment of Type 2 diabetes

Chemistry Review Data Sheet

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	Complete		Mei-yu Shen
EES	Pending		Office of Compliance
Pharm/Tox	N/A		David Carlson
Biopharm	N/A		Sang Chung
LNC	N/A		
Methods Validation	Not required at this time		Chien-Hua Niu
DMETS	Pending		
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, pending (1) satisfactory response to IR letter from applicant and (2) acceptable CGMP inspection of the manufacturing site for the drug product.

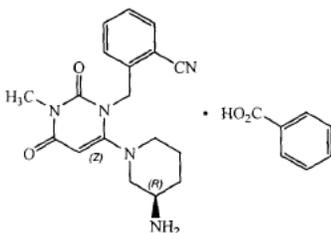
## B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

## II. Summary of Chemistry Assessments

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

Alogliptin is a highly potent and highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme that rapidly degrades incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). In patients with type 2 diabetes, levels of GLP-1 are reduced and the action of both GLP-1 and GIP are blunted. This markedly diminished incretin effect contributes to hyperglycemia. DPP-4 inhibition targets the incretin defect by increasing circulating blood levels of endogenous incretins, which increase insulin levels and decrease glucagon levels in a glucose-dependent manner. The increase in insulin levels enhances glucose uptake by tissues, and the decrease in glucagon levels reduces hepatic glucose production leading to improve glycemic controls.

**DRUG SUBSTANCE:** Alogliptin benzoate is designated chemically as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzotrile monobenzoate. The chemical structure and molecular formula for alogliptin benzoate are shown below:



Alogliptin benzoate is a new molecular entity manufactured by (b) (4). The API has one chiral center with stereochemical configuration of R. The manufacturing process for alogliptin benzoate is (b) (4).

## REVIEW NOTE

The structure of alogliptin was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ) spectroscopy, mass spectrometry, and X-ray crystallography. Alogliptin benzoate is a white to off-white crystalline powder, and decomposed with melting at approximately  $182.5^\circ\text{C}$ . It has a molecular weight of 416.51 (benzoate salt). It is highly soluble in DMSO, moderately soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate.

Results from X-ray diffraction studies demonstrate [REDACTED] (b) (4)

The proposed release specifications include appearance, identification (IR and UV), heavy metals, [REDACTED] (b) (4) assay, water content, assay, related substance, residual solvents, and particle size. The proposed regulatory methods have been validated. The impurities and degradation products have been investigated. Reference standard for API has been developed and characterized.

Based on data from ICH stability studies on 3 lots, alogliptin benzoate is stable [REDACTED] (b) (4)

**DRUG PRODUCT:** The proposed drug product is manufactured by Takeda Pharmaceutical Company Ltd (Osaka, Japan). NESINA tablets are available as film-coated immediate release tablets containing 6.25 mg, 12.5 mg or 25 mg of alogliptin as follows:

6.25 mg tablet: light pink, oval, biconvex, film-coated tablet, with "TAK ALG-6.25" printed on one side.

12.5 mg tablet: yellow, oval, biconvex, film-coated tablet, with "TAK ALG-12.5" printed on one side.

25 mg tablet: light red, oval, biconvex, film-coated tablet, with "TAK ALG-25" printed on one side.

NESINA tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate; the tablets are film-coated with hypromellose, titanium dioxide, ferric oxide (red and yellow), and polyethylene glycol, and marked with printing ink [REDACTED] (b) (4)

[REDACTED] All excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail.

NESINA tablets are manufactured [REDACTED] (b) (4)

[REDACTED] Finally, the film-coated tablets are printed [REDACTED] (b) (4) and packed into a suitable container.

The proposed release specifications include appearance, identification (UV and HPLC), assay (HPLC), related substances (HPLC), dissolution, and content uniformity. The proposed regulatory methods have been validated.

**REVIEW NOTE**

NASINA tablets (12.5 mg and 25 mg) are packaged in 7-count, 30-count, 90-count and 500-count high-density polyethylene (HDPE) bottles. These tablets are also packaged in 7-count (b)(4) foil blister. For 6.26 mg tablets, they are packaged in 30-count and 90-count HDPE bottles.

NESINA tablets packaged in different HDPE bottle configurations or blister package show no significant changes in terms of appearance, assay, related substances, dissolution, (b)(4) and hardness when stored at long term condition (25°C/60% RH) for 12 months and at accelerated conditions (40°C/75% RH). However, the (b)(4) degradation product has the relative retention time (RRT) of (b)(4). Levels for this related substance reached a (b)(4)

The photostability study indicates that NESINA tablets are not light sensitive.

Based on statistical analyses of stability data from samples packaged in HDPE bottles and blisters and stored at 25°C/60% RH for a period of 12 months, an expiration dating period (b)(4) is recommended for NESINA tablets.

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

Regarding comparability protocol, any changes in the manufacturing sites for the drug substance and drug product can be implemented after approval of a post-approval supplemental application for the NDA and a satisfactory CGMP status verified by the Office of Compliance of the FDA.

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

NESINA is an inhibitor of the dipeptide-peptidase-4 (DPP-4) enzyme and is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (type 2 diabetes). The recommended dose of NESINA is 25 mg once daily, as monotherapy or as combination therapy.

**C. Basis for Approvability or Not-Approval Recommendation:**

The recommendation that this application can be approved from a CMC viewpoint is based on the following: (1) The general procedures for the synthesis of alogliptin benzoate are outlined in the NDA. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Three primary stability batches for each dose strength of the 6.25 mg, 12.5 mg, and 25 mg Alogliptin Tablets have been manufactured by Takeda Pharmaceutical Company Ltd. at Osaka, Japan. All these batches were produced with the drug substance manufactured by (b)(4) and (4) Stability data for the drug product indicate that no significant changes were observed in terms of appearance, related substances, dissolution, assay, hardness, (b)(4), and microbial limit when stored at 25°C/60% RH for a period of 12 months and at 40°C/75% RH for 6 months.

**REVIEW NOTE**

**Pending Issue:** (1). Satisfactory response to IR letter from the applicant (2). CGMP inspection of the manufacturing sites for the drug product (Takeda Pharmaceutical Company Ltd., Osaka, Japan) has not been completed by the Office of Compliance.

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

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

Chemistry Branch Chief Name/Date: Ali Al Hakim, Ph.D. /ONDQA/DPMA-I/Branch-II

**C. CC Block**

Dr. Su Tran/Dr. Blair Fraser

Project Manager Name/Date: Julie Marchick, 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  
8/20/2008 12:25:48 PM  
CHEMIST  
CMC Review #1 for the Original Submission

Ali Al-Hakim  
8/20/2008 04:18:12 PM  
CHEMIST

**INITIAL QUALITY ASSESSMENT**  
**Office of New Drug Quality Assessment**  
**Division of Metabolism and Endocrinology Products (DMEP)**  
**NDA 22-271**

**APPLICANT INFORMATION:**

Applicant: Takeda Global Research & Development Center, Inc.  
One Takeda Parkway  
Deerfield, IL 60015-2235  
Tel. (224) 554-5391  
FAX (224) 554-7870

**Date of Submission:** Letter date 27-DEC-2007 (Received date: 27-DEC-2007)

**PRODUCT DESCRIPTION:**

**Proprietary Name:** NESINA™

**Established Name:** Alogliptin

**Dosage Form:** Tablets

**Strengths:** 6.25 mg, 12.5 mg, and 25 mg

**Route of Administration:** Oral

**Indication(s):** Type 2 Diabetes

**Drug Class:** Hypoglycemic agents, Oral II

**Remarks:** Alogliptin is an orally available, highly selective, and potent inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. DPP-4 inhibitors are a new class of antihyperglycemic agents for type 2 diabetes mellitus (T2DM), which prolong the activity of incretin hormones and thereby enhance insulin secretion and suppress glucagon secretion in a glucose-dependent manner. Alogliptin benzoate is a synthetic organic compound with one asymmetric carbon. Alogliptin benzoate is a new chemical entity (NCE). Alogliptin Tablets are for immediate release.

**APPLICATION DESCRIPTION:**

**Application Type:** 505(b)(1) NDA

**Proposed Marketing Status:** Rx

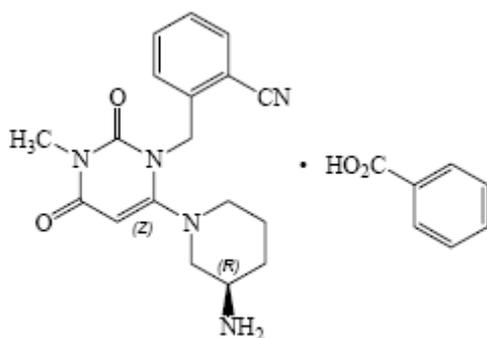
**Establishment Information:** None listed

**Cross-references:** None listed

## INITIAL QUALITY ASSESSMENT SUMMARY

**Drug Product Summary:** NESINA™ (alogliptin) Tablets contain the active ingredient alogliptin, which is a potent, selective, orally bioavailable inhibitor of the enzymatic activity of DPP-4. Each NESINA™ tablet is formulated to contain 25 mg, 12.5 mg, or 6.25 mg of alogliptin for oral administration. NESINA™ tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, and magnesium stearate; the tablets are film-coated with hypromellose, titanium dioxide, ferric oxide (red and yellow), and polyethylene glycol, and marked with printing ink (b) (4) NESINA™ tablets are for immediate release.

**Drug Substance Summary:** 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. Alogliptin benzoate is a synthetic organic compound with one asymmetric carbon. Alogliptin benzoate is a new chemical entity (NCE). It has a molecular formula of C<sub>18</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub>·C<sub>7</sub>H<sub>6</sub>O<sub>2</sub> and a molecular weight of 461.51; 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.

**Description of How the Drug Product is Intended to be Used:** NESINA™ is an inhibitor of the dipeptidyl-peptidase-4 (DPP-4) enzyme and is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (type 2 diabetes). NESINA™ is indicated for:

- Monotherapy
- Combination therapy, when the following agents do not provide adequate glycemic control:
  - a peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist (eg, thiazolidinediones), either alone or in combination with metformin or a sulfonylurea
  - metformin
  - a sulfonylurea
  - insulin, either alone or in combination with metformin

The recommended dose of NESINA™ is 25 mg once daily, as monotherapy or as combination therapy.



**Filability:** Acceptable for filing from CMC perspective.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?			N/A

Comment: The application was submitted in electronic copies. A conventional CMC summary is included in the application.

**Drug Master Files (DMFs):**

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA	PREVIOUS REVIEW(S)	RECOMMENDATION
(b) (4)	III	(b) (4)	(b) (4)	16-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	III		05-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		12-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		05-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		12-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		18-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*	
	III		14-NOV-2007	DMF previously reviewed, but not for particular item	<u>Review needed</u>	

(b) (4)	III	(b) (4)	18-OCT-2007	DMF previously reviewed, but not for particular item	<u>Review needed</u>
	III		16-OCT-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*
	IV		10-OCT-2007	DMF previously reviewed, but not for particular item	<u>Review needed</u>
	III		14-NOV-2007	DMF previously reviewed; Adequate information in NDA	Review not needed*

\*Review not needed in accordance with review policy for container-closure systems for solid oral dosage forms.

**Consults:**

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be assessed by Biopharm/ClinPharm reviewer.
CDRH	N/A
EA	Claim for Categorical Exclusion (< 1 PPB). To be assessed by primary CMC reviewer.
EES	EER submitted to Office of Compliance on 04/05-FEB-2008.
OSE/DMETS	Labeling consult request to be sent by DMEP
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	N/A
Pharm/Tox	To be assessed by Pharm/Tox reviewer.

**Recommendation for Primary CMC Reviewer(s):** Chien-Hua Niu, Ph.D. is recommended as the primary CMC reviewer.

**Identification of Critical CMC Review Issues:** See IQA notes and list of critical CMC review issues.

**Endorsement block (see appended electronic signature page):**

Stephen Moore, Ph.D., Pharmaceutical Assessment Lead (PAL), Branch II/DPA I/ONDQA

Init. by: Ali Al-Hakim, Ph.D., Branch Chief, Branch II/DPA I/ONDQA

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Stephen Moore  
2/12/2008 04:57:55 PM  
CHEMIST

Ali Al-Hakim  
2/12/2008 05:12:43 PM  
CHEMIST