

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022426Orig1s000**

**CHEMISTRY REVIEW(S)**

## Memorandum to NDA 22426 File

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

Date: January 22, 2013

Subject: Office of Compliance **Acceptable** Recommendation for the Facilities Associated With NDA 22426

Drug Product Name/Strength: Oseni® (alogliptin and pioglitazone) Tablets/  
25/15 mg, 25/45 mg, 12.5/15 mg, 12.5/30mg, 12.5/45 mg

Ref.: Previous CMC review dated 12/12/12 for NDA 22426 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 are **Acceptable**. Therefore, from both CMC perspective and Office of Compliance point of view, this NDA (22426) 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 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 |           |            |

**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

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**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

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**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

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**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

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**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

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**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

**SUMMARY REPORT**

**Establishment:** CFN: [REDACTED] FEI: [REDACTED] (b) (4)  
[REDACTED] (b) (4)  
**DMF No:** [REDACTED] **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:** [REDACTED] **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:** [REDACTED] **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: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)  
[REDACTED] (b) (4)  
**DMF No:** [REDACTED] **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

# 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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/s/  
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MUTHUKUMAR RAMASWAMY  
12/12/2012

ALI H AL HAKIM  
12/12/2012

**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)<br><br>-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> |
|---|--------------------------|--|

| 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.”

---

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.

---

**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:

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

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  $\text{(b) (4)}$   $\text{(b) (4)}$  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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/s/  
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JOHN C HILL  
01/04/2012

ALI H AL HAKIM  
01/04/2012

(b) (4)

**(Alogliptin/Pioglitazone) tablets**  
**NDA 22-426**

**Summary of the Basis for the Recommended Action  
from 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:** The drug product is (b) (4) film-coated, immediate-release tablets. The proposed dosage forms and strengths (free base alogliptin/ free base pioglitazone) are:

- 25 mg/15 mg tablets are yellow, round, biconvex, film-coated tablets, with both “A/P” and “25/15” printed on one side.
- 25 mg/30 mg tablets are peach, round, biconvex, film-coated tablets, with both “A/P” and “25/30” printed on one side.
- 25 mg/45 mg tablets are red, round, biconvex, film-coated tablets, with both “A/P” and “25/45” printed on one side.
- 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.
- 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.
- 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.

Tablets of the drug product are provided in both physician samples and commercial package configurations. 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.

**EER Status:** **Withhold** – M. Stock – 15 – July -2009

**Consults:** EA – Categorical exclusion granted under 21 CFR 25.31  
Methods Validation – Revalidation by Agency was not requested  
Biopharm – Acceptable, with Phase IV agreement – T. Ghosh – 4- Jun-2009

**Original Submission:** 19-Sept- 2008

**Re-submissions:** N/A

**Post-Approval CMC Agreements:** None

**Background:**

This application was filed as a 505(b)(1) application (reference is made to the pending NDA 22-271 for alogliptin, which is a New Molecular Entity).

**Drug Substance:**

There are two drug substances for this NDA; alogliptin benzoate and pioglitazone hydrochloride. All chemistry, manufacturing and controls information for each drug substance is contained in NDA 22-271 for alogliptin benzoate and NDA 21-073 for pioglitazone hydrochloride. NDA 21-073 was approved in 1999 for the Actos® marketed single-entity pioglitazone hydrochloride drug product. NDA 22-271 has not yet been approved (Complete Response action on 26-Jun-2009 for clinical and nonclinical deficiencies) but is recommended for approval by CMC. No other issues have been identified that would affect the use of the APIs in the proposed fixed-dose combination product.

**Conclusion:** The drug substance information is satisfactory.

**Drug Product:**

Alogliptin/pioglitazone is a fixed-dose combination oral product composed of two active ingredients, alogliptin benzoate and pioglitazone hydrochloride, formulated as (b) (4) film-coated, immediate-release tablets. Each drug product is a (u) (4) film-coated, immediate-release tablet intended to provide a single tablet with a clinical effect bioequivalent to the administration of two single entity immediate release tablets each containing the same doses of the respective drugs. The dosage strengths in the fixed dose combination product are 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone.

The manufacturing process consists (b) (4)

The excipients are mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hypromellose (b) (4), polyethylene glycol (b) (4), titanium dioxide, talc, ferric oxide (yellow and/or red), and printing ink (Red A1 or Gray F1). The proposed release specifications include appearance, identification (UV and HPLC), assay (HPLC), dissolution, related substances and content uniformity. Based on the available real time stability data

provided for the drug product stored at 25°C, 24 months of expiry dating is granted for the drug product.

**Conclusion:** The drug product information is satisfactory.

**Additional Items:**

- The Office of Compliance issued an overall Withhold recommendation, based on inspection of the one of the drug substance manufacturers for pioglitazone (b) (4) [REDACTED]
- The applicant has agreed to revise the drug product dissolution test method and specification within 1 year from the date of approval.
- The applicant has agreed to complete 60-month long term and 6-month accelerated stability studies for 3 pilot-scale and the first 3 commercial lots of the drug product. In addition, the applicant agrees to add one commercial lot to the stability program each year following approval.
- The applicant agreed to revisit the specifications for related substances in the drug product after obtaining additional experience with the commercial manufacturing process.
- All associated Drug master Files are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

**Overall Conclusion:**

**The application cannot be recommended for approval** from a CMC perspective because of Withhold recommendation issued by the Office of Compliance on July 15, 2009.

Christine M. V. Moore, Ph.D.  
DPA I Director (acting)  
ONDQA/CDER/FDA

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/s/

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Christine Moore  
7/21/2009 12:44:10 PM  
CHEMIST

**NDA 22-426**

(b) (4)

**(Alogliptin/Pioglitazone) Tablets**

**Takeda Global Research and Development Center,  
Incorporated**

**Theodore Carver**  
**Division of Pre-Marketing Assessment I, ONDQA**  
**and**  
**Division of Metabolism and Endocrine Drug Products**

# Table of Contents

|   |           |
|---|-----------|
| <b>Table of Contents .....</b>  | <b>2</b>  |
| <b>Chemistry Review Data Sheet.....</b>   | <b>3</b>  |
| <b>The Executive Summary .....</b>  | <b>8</b>  |
| <b>I. Recommendations .....</b>   | <b>8</b>  |
| A. Recommendation and Conclusion on Approvability .....   | 8         |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8         |
| <b>II. Summary of Chemistry Assessments .....</b>   | <b>8</b>  |
| A. Description of the Drug Product(s) and Drug Substance(s) .....   | 8         |
| C. Basis for Approvability or Not-Approval Recommendation.....  | 11        |
| <b>III. Administrative.....</b>   | <b>11</b> |
| A. Reviewer's Signature.....  | 11        |
| B. Endorsement Block.....   | 11        |
| C. CC Block .....   | 12        |



# Chemistry Review Data Sheet

1. NDA 22-426
2. REVIEW #:3
3. REVIEW DATE: 7/16/2009
4. REVIEWER: Theodore Carver
5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u>                              | <u>Document Date</u> |
|--|----------------------|
| Original NDA   | 9-19-2008            |
| Amendment (Response to 74-day letter)                  | 1-28-2009            |
| Amendment seq. no. 008 (Amended Stability Data)        | 03-30-2009           |
| Amendment seq.no. 011 (Response to 4/3/2009 IR Letter) | 05/20/2009           |
| Amendment seq.no. 014                                  | 05/29/2009           |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u>     | <u>Document Date</u> |
|-----------------------------------|----------------------|
| N/A (update on OC recommendation) |                      |

7. NAME & ADDRESS OF APPLICANT:

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



Executive Summary Section

Telephone:

(847) 582-3504

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:                      (b) (4)
- b) Non-Proprietary Name (USAN): Alogliptin/Pioglitazone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only): n/a

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: anti-diabetic

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: Alogliptin/Pioglitazone (free base/free base): 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg, 12.5 mg/ 15 mg, 12.5 mg/ 30 mg, and 12.5 mg/45 mg

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

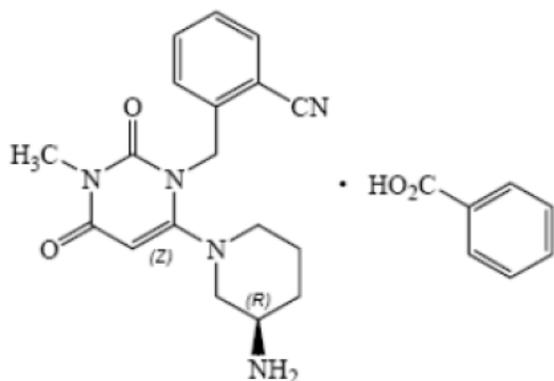
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Executive Summary Section

**a. Alogliptin Benzoate**Chemical Name(s):

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

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

Structural Formula (absolute stereochemistry):

Molecular Formula:  $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$

Molecular Weight:

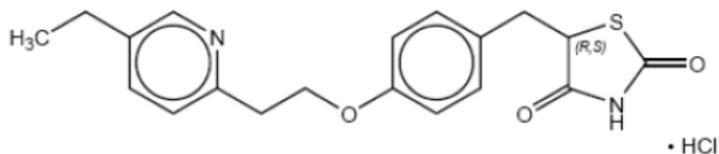
461.51 (benzoate salt)

339.39 (free base)

**b. Pioglitazone Hydrochloride**Chemical Names(s):

(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

## Executive Summary Section

Structural Formula:Molecular Formula: C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S . HClMolecular Weight:

392.90 (HCl salt)

356.43 (free base)

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

| DMF #   | TYPE | HOLDER  | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) | III  | (b) (4) | (b) (4)         | 4                 | Adequate            |                       |          |
|         | III  |         |                 | 3                 | Adequate            | 12/07/2004            |          |
|         | III  |         |                 | 4                 | Adequate            |                       |          |
|         | III  |         |                 | 3                 | Adequate            | 10/16/2007            |          |
|         | III  |         |                 | 4                 | Adequate            | 3/11/2005             |          |
|         | III  |         |                 | 3                 | Adequate            | 12/22/2008            |          |
|         | III  |         |                 | 3                 | Adequate            | 6/20/2006             |          |
|         | III  |         |                 | 4                 | Adequate            | 11/19/2007            |          |
|         | III  |         |                 | 3                 | Adequate            | 8/4/2008              |          |

Executive Summary Section

<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  |
|----------|--------------------|--|
| NDA      | 22-271             | Nesina® (Alogliptin); referenced for drug substance  |
| NDA      | 21-073             | Actos® (Pioglitazone); referenced for drug substance |

**18. STATUS:**

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                               | DATE | REVIEWER             |
|-------------------------------|--|------|----------------------|
| Biometrics                    | n/a  |      |                      |
| EES                           | Withhold                                     |      | Office of Compliance |
| Pharm/Tox                     | Acceptable                                   |      | David Carlson        |
| Biopharm                      | Acceptable                                   |      | Tapash Ghosh         |
| LNC                           | n/a  |      |                      |
| Methods Validation            | n/a, according to current ONDQA policy       |      |                      |
| OSE                           | Acceptable                                   |      | DMEPA and DDMAC      |
| EA                            | Adequate – request for categorical exclusion |      | Theodore Carver      |
| Microbiology                  | n/a  |      |                      |

# The Chemistry Review for NDA 22-426

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC recommendation is non-approval, based on the overall recommendation of Withhold from the Office of Compliance.

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

The applicant has made the following agreements during the course of the review of this NDA (these agreements are not commitments/requirements and will NOT be included in the Action Letter):

A standard stability agreement. The applicant has agreed to complete 60-month long-term and 6-month accelerated stability studies for 3 pilot-scale and the first 3 commercial lots of the drug product. In addition, the applicant agrees to add one commercial lot to the stability program each year following approval.

An agreement to revisit the specifications for related substances in the drug product after obtaining additional experience with the commercial manufacturing process.

A Phase IV agreement to revise the drug product dissolution test method and specification within 1 year from the date of approval, if appropriate.

### II. Summary of Chemistry Assessments

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

##### Drug Substance:

All chemistry, manufacturing and controls information for each drug substance is contained in NDA 22-271 for alogliptin benzoate and NDA 21-073 for pioglitazone hydrochloride. NDA 22-271, for the single-entity alogliptin tablet, is currently under review, but has been recommended for approval by CMC and all outstanding CMC issues have been resolved.

Alogliptin benzoate is a new molecular entity not yet approved as a single entity tablet.

Alogliptin benzoate is a white to off-white crystalline powder, melting at 182.5°C, that is sparingly to moderately soluble over a wide range of pH (21.3 mg/mL at pH 7.0). The API has a single chiral center and is prepared as the R-enantiomer. The manufacturer for alogliptin benzoate is

benzoate is (b) (4) The manufacturing process for alogliptin benzoate is (b) (4)

## Executive Summary Section

(b) (4) The structure has been suitably characterized by elemental analysis, UV and IR spectroscopy, NMR spectroscopy ( $^1\text{H}$  and  $^{13}\text{C}$ ), mass spectrometry, and X-ray crystallography. (b) (4)

The proposed release specifications include appearance, identification (IR and UV), heavy metals, (b) (4) water content, assay, related substance, residual solvents, and particle size. Clarification has been requested from the applicant regarding the proposed particle size specification, in light of API batch data. No other issues have been identified that will affect the use of this API in the proposed fixed-dose combination product. Although NDA 22-271 has been recommended for approval by CMC, CMC issues that may arise in either the single-entity or fixed dose combination product applications should be monitored as review of both applications continues.

Pioglitazone HCl is an approved drug in single-entity tablets, approved in 1999. Pioglitazone HCl is a white crystalline product that is sparingly soluble to practically insoluble above pH 2.0 (0.00093 mg/mL at pH 7.0). The API is a racemic mixture. Manufacture is (b) (4)

(b) (4) The structure has been suitably characterized by elemental analysis, UV and IR spectroscopy, NMR spectroscopy ( $^1\text{H}$  and  $^{13}\text{C}$ ), and mass spectrometry. The pioglitazone HCl drug substance is well characterized with a 10-year manufacturing history since approval. The in-process controls and impurities profiles are well-defined and there is no history of significant issues with the manufacturing process. NDA 21-073 is an approved NDA for the Actos® marketed single-entity pioglitazone hydrochloride drug product.

Drug Product:

Alogliptin/pioglitazone is a fixed-dose combination oral product composed of two active ingredients, alogliptin benzoate and pioglitazone hydrochloride, formulated as (b) (4) film-coated, immediate-release tablets. The proposed drug product is intended to provide a single tablet with a clinical effect bioequivalent to the administration of two single-entity immediate release tablets each containing the same doses of the respective drugs. (b) (4)

(b) (4) The dose strengths in the fixed-dose combination product are 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone. The maximum daily dose is 25 mg alogliptin (free base)/45 mg pioglitazone (free base).

The proposed dosage forms and strengths are:

## Executive Summary Section

- 25 mg/15 mg tablets are yellow, round, biconvex, film-coated tablets, with both “A/P” and “25/15” printed on one side.
- 25 mg/30 mg tablets are peach, round, biconvex, film-coated tablets, with both “A/P” and “25/30” printed on one side.
- 25 mg/45 mg tablets are red, round, biconvex, film-coated tablets, with both “A/P” and “25/45” printed on one side.
- 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.
- 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.
- 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.

The excipients are mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hypromellose (b) (4) polyethylene glycol (b) (4), titanium dioxide, talc, ferric oxide (yellow and/or red), and printing ink (Red A1 or Gray F1). The proposed release specifications include appearance, identification (UV and HPLC), assay (HPLC), dissolution, and content uniformity. We requested that the applicant include a related substances assay (HPLC) in the drug product release specification. The new drug product specifications for each dosage strength, including related substances testing for alogliptin, were submitted in the amendment received on 5/29/09. The proposed regulatory methods have been validated.

6 months long-term and 6 months accelerated stability data were supplied in the original NDA submission. Applicant obtained agreement from the FDA to submit 12 months long term stability data no later than 3 months prior to the PDUFA goal date for this application, and this requirement was fulfilled in the amendment received 3/30/2009. Applicant has requested 24 months shelf life, which is granted, based upon the ICH Q1E guideline and the results of stability studies to date.

**B. Description of how the drug product is intended to be used**

(b) (4) (alogliptin/pioglitazone) is a fixed dose combination product consisting of two anti-diabetic drugs that function according to different mechanisms. Pioglitazone HCl belongs to the thiazolidinedione class of drugs, which activate peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) receptors. PPAR $\gamma$  receptors regulate the transcription of genes linked to insulin activation; therefore, activation of these receptors in target tissues effectively bypasses the defective insulin signaling resulting from insulin resistance. Alogliptin benzoate is a dipeptidyl peptidase IV inhibitor. DPP-IV rapidly degrades incretins, such as GLP-1 and GIP. Since incretin levels are lower in diabetic patients, artificially increasing their levels by inhibiting DPP-IV improves glycemic control by elevating insulin levels and reducing glucagon levels. Thus, whereas pioglitazone improves glycemic control intracellularly by bypassing insulin signaling in diabetic patients, the other drug improves glycemic control extracellularly by increasing the

## Executive Summary Section

signaling due to insulin and other hormones involved in glycemic control. Patients whose diabetes is not adequately controlled by either drug alone may benefit from taking both drugs in combination, since they operate by different mechanisms. By providing six different dosage strengths of both drugs, the fixed dose combination product facilitates management of Type II diabetes with a single tablet in patients that benefit from receiving both drugs. The maximum daily dose is 25/45 mg/mg (free base/free base) alogliptin/pioglitazone. Bioequivalence studies were conducted with the highest and lowest strengths, 12.5/15 and 25/45. A biowaiver request is made for the other strengths.

Tablets of the drug product are provided in both professional samples and commercial package configurations. 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.

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

All outstanding CMC issues raised in Chem. Rev. #1 by this reviewer have been resolved by the applicant in amendments subsequent to the original NDA as discussed in this Chem. Rev. #2.

The applicant obtained agreement from the FDA to submit 12 months of long-term stability data no later than 3 months prior to the goal date for the original NDA submission. These stability data were submitted by the applicant in an amendment, evaluated in this review, and found acceptable. Therefore a 24-month shelf life is granted for this product. In a separate amendment the applicant submitted additional information and data in response to the CMC IR letter. The applicants response to each comment was satisfactory.

The applicant submitted a Phase IV agreement to revise the drug product dissolution test method and specification within 1 year from date of approval. This agreement was the subject of a CMC memo-to-file dated 6/18/2009 and was found to satisfactorily address all outstanding biopharmaceutics issues.

The final CMC recommendation of non-approval is based upon the overall recommendation of Withhold from the Office of Compliance.

**III. Administrative****A. Reviewer's Signature**

\_\_\_\_\_  
Theodore Carver, CMC Reviewer, ONDQA/PMA Division I

**B. Endorsement Block**

T. Carver/CMC Reviewer, 06/11/09



## CHEMISTRY REVIEW



### Executive Summary Section

A. Al-Hakim/Team Leader, 06/11/09

**C. CC Block**

Suong Tran/CMC Lead, 06/11/09

Julie Marchick/RPM, 06/11/09

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this 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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Theodore Carver  
7/16/2009 02:35:33 PM  
CHEMIST  
CMC recommendation of non-approval based on OC Withhold recommendation

Ali Al-Hakim  
7/16/2009 02:55:26 PM  
CHEMIST

## MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drug Quality Assessment

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**DATE:** June 18, 2009

**FROM:** Theodore Carver, Ph.D.  
Branch II, DPA I, ONDQA

**SUBJECT:** Phase IV Agreement for NDA 22-246  
(b) (4) Alogliptin/Pioglitazone tablets

**TO:** NDA 22-426 file

The applicant has submitted a Phase IV agreement, shown below, to revise the drug product dissolution test method and specification within 1 year from the date of approval, if appropriate. This agreement is a satisfactory response to issues raised by the biopharmaceutics review. Therefore, **the only pending CMC issue for this NDA is a recommendation from the Office of Compliance.**

Applicant's Phase IV Agreement to Revise Dissolution Test Method for SYR-322-4833 Tablets and Pioglitazone Dissolution Specification:

Based on a comment received from FDA (CMC information request letter dated 09 June 2009) and a follow-up e-mail request received on 17 June 2009, TGRD will further evaluate a change in the analytical procedure for dissolution of SYR-322-4833 tablets (changing paddle speed (b) (4) to 50 rpm), with the intent of implementing the change to the commercial testing method within 1 year after product approval. In the interim, additional dissolution profile data will be gathered and method validation performed to evaluate and confirm the appropriateness of the 50 rpm paddle speed along with the previously agreed upon specification of  $Q = (b) (4)$  in 30 minutes for pioglitazone.

Assuming the additional 50 rpm data confirms that the method is reliable and compatible with the agreed specifications, the method change will be implemented and reported in the first NDA Annual Report after approval. The method including this change is summarized as follows:

Medium: 900 mL of pH 2.2 Sørensen buffer (without deaeration) Apparatus 2, paddle speed 50 rpm  
Temperature: 37°C ± 0.5°C

Supporting documents to be included in the Annual Report are the revised analytical procedure and validation report for dissolution (Sections 3.2.P.5.2 and 3.2.P.5.3).

Until implementation of this change, product release and stability testing will continue with the originally proposed (b) (4) method.

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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/

-----  
Theodore Carver  
6/18/2009 04:32:04 PM  
CHEMIST  
Closes out biopharm dissolution test and specificaiton issues.

Ali Al-Hakim  
6/18/2009 04:46:21 PM  
CHEMIST

**NDA 22-426**

(b) (4)

**(Alogliptin/Pioglitazone) Tablets**

**Takeda Global Research and Development Center,  
Incorporated**

**Theodore Carver  
Division of Pre-Marketing Assessment I, ONDQA  
and  
Division of Metabolism and Endocrine Drug Products**

# Table of Contents

|   |           |
|---|-----------|
| <b>Table of Contents .....</b>  | <b>2</b>  |
| <b>Chemistry Review Data Sheet.....</b>   | <b>3</b>  |
| <b>The Executive Summary .....</b>  | <b>8</b>  |
| I. Recommendations .....  | 8         |
| A. Recommendation and Conclusion on Approvability .....   | 8         |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8         |
| II. Summary of Chemistry Assessments .....  | 8         |
| A. Description of the Drug Product(s) and Drug Substance(s) .....   | 8         |
| C. Basis for Approvability or Not-Approval Recommendation.....  | 11        |
| III. Administrative.....  | 11        |
| A. Reviewer's Signature.....  | 11        |
| B. Endorsement Block.....   | 11        |
| C. CC Block .....   | 12        |
| <b>Chemistry Assessment .....</b>   | <b>13</b> |

# Chemistry Review Data Sheet

1. NDA 22-426

2. REVIEW #:2

3. REVIEW DATE: 6/10/2009

4. REVIEWER: Theodore Carver

5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u>             | <u>Document Date</u> |
|---------------------------------------|----------------------|
| Original NDA                          | 9-19-2008            |
| Amendment (Response to 74-day letter) | 1-28-2009            |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u>                          | <u>Document Date</u> |
|--|----------------------|
| Amendment seq. no. 008 (Amended Stability Data)        | 03-30-2009           |
| Amendment seq.no. 011 (Response to 4/3/2009 IR Letter) | 05/20/2009           |
| Amendment seq.no. 014                                  | 05/29/2009           |

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Global Research and Development, Inc.

Address: One Takeda Parkway, Deerfield, IL 60015-2235

Representative:

## Chemistry Review Data Sheet

Telephone:

(847) 582-3504

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

- a) Proprietary Name: (b) (4)  
b) Non-Proprietary Name (USAN): Alogliptin/Pioglitazone  
c) Code Name/# (ONDC only): N/A  
d) Chem. Type/Submission Priority (ONDC only): n/a

## 9. LEGAL BASIS FOR SUBMISSION: Not applicable

## 10. PHARMACOL. CATEGORY: anti-diabetic

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: Alogliptin/Pioglitazone (free base/free base): 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg, 12.5 mg/ 15 mg, 12.5 mg/ 30 mg, and 12.5 mg/45 mg

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

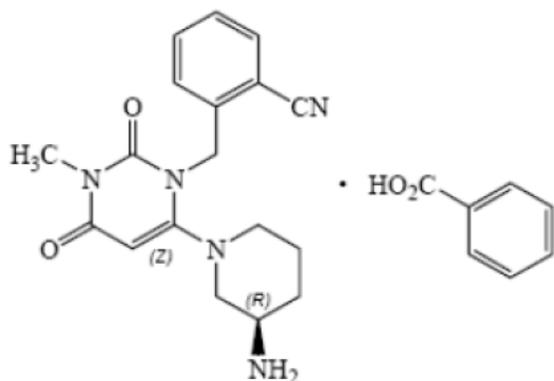
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

**a. Alogliptin Benzoate**Chemical Name(s):

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

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

Structural Formula (absolute stereochemistry):

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:

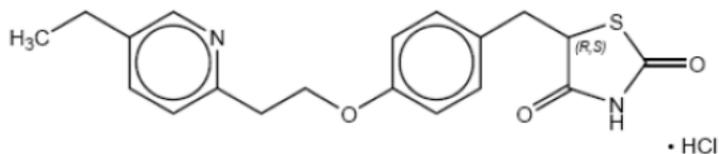
461.51 (benzoate salt)

339.39 (free base)

**b. Pioglitazone Hydrochloride**Chemical Names(s):

(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

## Chemistry Review Data Sheet

Structural Formula:Molecular Formula: C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S · HClMolecular Weight:

392.90 (HCl salt)

356.43 (free base)

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

| DMF #   | TYPE | HOLDER  | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) | III  | (b) (4) | (b) (4)         | 4                 | Adequate            |                       |          |
|         | III  |         |                 | 3                 | Adequate            | 12/07/2004            |          |
|         | III  |         |                 | 4                 | Adequate            |                       |          |
|         | III  |         |                 | 3                 | Adequate            | 10/16/2007            |          |
|         | III  |         |                 | 4                 | Adequate            | 3/11/2005             |          |
|         | III  |         |                 | 3                 | Adequate            | 12/22/2008            |          |
|         | III  |         |                 | 3                 | Adequate            | 6/20/2006             |          |
|         | III  |         |                 | 4                 | Adequate            | 11/19/2007            |          |
|         | III  |         |                 | 3                 | Adequate            | 8/4/2008              |          |

Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

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**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION  |
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| NDA      | 21-073             | Actos® (Pioglitazone); referenced for drug substance |

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                               | DATE | REVIEWER             |
|-------------------------------|--|------|----------------------|
| Biometrics                    | n/a  |      |                      |
| EES                           | pending                                      |      | Office of Compliance |
| Pharm/Tox                     | n/a  |      |                      |
| Biopharm                      | pending                                      |      | Tapash Ghosh         |
| LNC                           | n/a  |      |                      |
| Methods Validation            | n/a  |      |                      |
| OSE                           | pending                                      |      | DMEPA and DDMAC      |
| EA                            | Adequate – request for categorical exclusion |      | Theodore Carver      |
| Microbiology                  | n/a  |      |                      |

# The Chemistry Review for NDA 22-426

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC recommendation is approval, pending the overall recommendation from the Office of Compliance (completion of establishment inspections) and the final recommendation of the ONDQA biopharmaceutics reviewer (biowaiver for the 25/15, 25/30, 12.5/30, and 12.5/45 mg/mg alogliptin/pioglitazone strengths). All outstanding CMC issues raised in Chem. Rev. #1 by this reviewer have been adequately addressed by the applicant as discussed in this Chem. Rev. #2.

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

The applicant has made the following agreements during the course of the review of this NDA (these agreements are not commitments/requirements and will NOT be included in the Action Letter):

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

##### Drug Substance:

All chemistry, manufacturing and controls information for each drug substance is contained in NDA 22-271 for alogliptin benzoate and NDA 21-073 for pioglitazone hydrochloride. NDA 22-271, for the single-entity alogliptin tablet, is currently under review, but has been recommended for approval by CMC and all outstanding CMC issues have been resolved.

Alogliptin benzoate is a new molecular entity not yet approved as a single entity tablet. Alogliptin benzoate is a white to off-white crystalline powder, melting at 182.5°C, that is sparingly to moderately soluble over a wide range of pH (21.3 mg/mL at pH 7.0). The API has a single chiral center and is prepared as the R-enantiomer. The manufacturer for alogliptin benzoate is (b) (4). The manufacturing process for alogliptin benzoate is (b) (4).

## Executive Summary Section

(b) (4) The structure has been suitably characterized by elemental analysis, UV and IR spectroscopy, NMR spectroscopy ( $^1\text{H}$  and  $^{13}\text{C}$ ), mass spectrometry, and X-ray crystallography. (b) (4)

The proposed release specifications include appearance, identification (IR and UV), heavy metals, (b) (4) water content, assay, related substance, residual solvents, and particle size. Clarification has been requested from the applicant regarding the proposed particle size specification, in light of API batch data. No other issues have been identified that will affect the use of this API in the proposed fixed-dose combination product. Although NDA 22-271 has been recommended for approval by CMC, CMC issues that may arise in either the single-entity or fixed dose combination product applications should be monitored as review of both applications continues.

Pioglitazone HCl is an approved drug in single-entity tablets, approved in 1999. Pioglitazone HCl is a white crystalline product that is sparingly soluble to practically insoluble above pH 2.0 (0.00093 mg/mL at pH 7.0). The API is a racemic mixture. Manufacture is (b) (4)

(b) (4) The structure has been suitably characterized by elemental analysis, UV and IR spectroscopy, NMR spectroscopy ( $^1\text{H}$  and  $^{13}\text{C}$ ), and mass spectrometry. The pioglitazone HCl drug substance is well characterized with a 10-year manufacturing history since approval. The in-process controls and impurities profiles are well-defined and there is no history of significant issues with the manufacturing process. NDA 21-073 is an approved NDA for the Actos® marketed single-entity pioglitazone hydrochloride drug product.

Drug Product:

Alogliptin/pioglitazone is a fixed-dose combination oral product composed of two active ingredients, alogliptin benzoate and pioglitazone hydrochloride, formulated as (b) (4) film-coated, immediate-release tablets. The proposed drug product is intended to provide a single tablet with a clinical effect bioequivalent to the administration of two single-entity immediate release tablets each containing the same doses of the respective drugs. (b) (4)

(b) (4) The dose strengths in the fixed-dose combination product are 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone. The maximum daily dose is 25 mg alogliptin (free base)/45 mg pioglitazone (free base).

The proposed dosage forms and strengths are:

## Executive Summary Section

- 25 mg/15 mg tablets are yellow, round, biconvex, film-coated tablets, with both “A/P” and “25/15” printed on one side.
- 25 mg/30 mg tablets are peach, round, biconvex, film-coated tablets, with both “A/P” and “25/30” printed on one side.
- 25 mg/45 mg tablets are red, round, biconvex, film-coated tablets, with both “A/P” and “25/45” printed on one side.
- 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.
- 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.
- 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.

The excipients are mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hypromellose (b) (4), polyethylene glycol (b) (4), titanium dioxide, talc, ferric oxide (yellow and/or red), and printing ink (Red A1 or Gray F1). The proposed release specifications include appearance, identification (UV and HPLC), assay (HPLC), dissolution, and content uniformity. We requested that the applicant include a related substances assay (HPLC) in the drug product release specification. The new drug product specifications for each dosage strength, including related substances testing for alogliptin, were submitted in the amendment received on 5/29/09. The proposed regulatory methods have been validated.

6 months long-term and 6 months accelerated stability data were supplied in the original NDA submission. Applicant obtained agreement from the FDA to submit 12 months long term stability data no later than 3 months prior to the PDUFA goal date for this application, and this requirement was fulfilled in the amendment received 3/30/2009. Applicant has requested 24 months shelf life, which is granted, based upon the ICH Q1E guideline and the results of stability studies to date.

**B. Description of how the drug product is intended to be used**

(b) (4) (alogliptin/pioglitazone) is a fixed dose combination product consisting of two anti-diabetic drugs that function according to different mechanisms. Pioglitazone HCl belongs to the thiazolidinedione class of drugs, which activate peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) receptors. PPAR $\gamma$  receptors regulate the transcription of genes linked to insulin activation; therefore, activation of these receptors in target tissues effectively bypasses the defective insulin signaling resulting from insulin resistance. Alogliptin benzoate is a dipeptidyl peptidase IV inhibitor. DPP-IV rapidly degrades incretins, such as GLP-1 and GIP. Since incretin levels are lower in diabetic patients, artificially increasing their levels by inhibiting DPP-IV improves glycemic control by elevating insulin levels and reducing glucagon levels. Thus, whereas pioglitazone improves glycemic control intracellularly by bypassing insulin signaling in diabetic patients, the other drug improves glycemic control extracellularly by increasing the

## Executive Summary Section

signaling due to insulin and other hormones involved in glycemic control. Patients whose diabetes is not adequately controlled by either drug alone may benefit from taking both drugs in combination, since they operate by different mechanisms. By providing six different dosage strengths of both drugs, the fixed dose combination product facilitates management of Type II diabetes with a single tablet in patients that benefit from receiving both drugs. The maximum daily dose is 25/45 mg/mg (free base/free base) alogliptin/pioglitazone. Bioequivalence studies were conducted with the highest and lowest strengths, 12.5/15 and 25/45. A biowaiver request is made for the other strengths.

Tablets of the drug product are provided in both professional samples and commercial package configurations. 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.

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

All outstanding CMC issues raised in Chem. Rev. #1 by this reviewer have been resolved by the applicant in amendments subsequent to the original NDA as discussed in this Chem. Rev. #2.

The applicant obtained agreement from the FDA to submit 12 months of long-term stability data no later than 3 months prior to the goal date for the original NDA submission. These stability data were submitted by the applicant in an amendment, evaluated in this review, and found acceptable. Therefore a 24-month shelf life is granted for this product. In a separate amendment the applicant submitted additional information and data in response to the CMC IR letter. The applicants response to each comment was satisfactory, therefore approval of the CMC portion of this NDA as reviewed in Chem. Rev. #1 and #2 by this reviewer is recommended.

The ONDQA biopharmaceutics recommendation (biowaiver for the 25/15, 25/30, 12.5/30, and 12.5/45 mg/mg alogliptin/pioglitazone strengths) will be filed separately and is not included in this final CMC review.

The Office of Compliance has not made a final determination of the cGMP status of the manufacturing and testing facilities for this NDA.

**III. Administrative****A. Reviewer's Signature**

\_\_\_\_\_  
Theodore Carver, CMC Reviewer, ONDQA/PMA Division I

**B. Endorsement Block**

T. Carver/CMC Reviewer, 06/11/09

## Executive Summary Section

A. Al-Hakim/Team Leader, 06/11/09

**C. CC Block**

Suong Tran/CMC Lead, 06/11/09

Julie Marchick/RPM, 06/11/09

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/s/

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Theodore Carver  
6/11/2009 08:27:22 PM  
CHEMIST

Approval recommended by CMC peinding OC and ONDQA biopharmceutics  
recommendations

Ali Al-Hakim  
6/12/2009 10:42:22 AM  
CHEMIST

**NDA 22-426**

(b) (4)

**(Alogliptin/Pioglitazone) Tablets**

**Takeda Global Research and Development Center,  
Incorporated**

**Theodore Carver**  
**Division of Pre-Marketing Assessment I, ONDQA**  
**and**  
**Division of Metabolism and Endocrine Drug Products**

# Table of Contents

|   |           |
|---|-----------|
| <b>Table of Contents .....</b>  | <b>2</b>  |
| <b>Chemistry Review Data Sheet.....</b>   | <b>3</b>  |
| <b>The Executive Summary .....</b>  | <b>8</b>  |
| I. Recommendations .....  | 8         |
| A. Recommendation and Conclusion on Approvability .....   | 8         |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8         |
| II. Summary of Chemistry Assessments.....   | 8         |
| A. Description of the Drug Product(s) and Drug Substance(s) .....   | 8         |
| C. Basis for Approvability or Not-Approval Recommendation.....  | 11        |
| III. Administrative.....  | 11        |
| A. Reviewer's Signature.....  | 11        |
| B. Endorsement Block.....   | 11        |
| C. CC Block .....   | 11        |
| <b>Chemistry Assessment .....</b>   | <b>12</b> |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....                                    | 12        |
| S DRUG SUBSTANCE [alogliptin/pioglitazone, Takeda] .....  | 12        |
| P DRUG PRODUCT [alogliptin/pioglitazone, Takeda] .....  | 37        |
| A APPENDICES .....  | 92        |
| R REGIONAL INFORMATION .....  | 93        |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....  | 93        |
| A. Labeling & Package Insert .....  | 93        |
| B. Environmental Assessment Or Claim Of Categorical Exclusion .....   | 99        |
| III. List Of Deficiencies To Be Communicated.....   | 99        |

# Chemistry Review Data Sheet

1. NDA 22-426

2. REVIEW #:1

3. REVIEW DATE: 3/30/2009

4. REVIEWER: Theodore Carver

5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

n/a

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original submission

09-19-2008

Amendment (Response to 74-day letter)

01-28-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Takeda Global Research and Development, Inc.

Address: One Takeda Parkway, Deerfield, IL 60015-2235

Representative:

Telephone: (847) 582-3504

## Chemistry Review Data Sheet

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

- a) Proprietary Name: (b) (4)  
b) Non-Proprietary Name (USAN): Alogliptin/Pioglitazone  
c) Code Name/# (ONDC only): N/A  
d) Chem. Type/Submission Priority (ONDC only): n/a

## 9. LEGAL BASIS FOR SUBMISSION: Not applicable

## 10. PHARMACOL. CATEGORY: anti-diabetic

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: Alogliptin/Pioglitazone (free base/free base): 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg, 12.5 mg/ 15 mg, 12.5 mg/ 30 mg, and 12.5 mg/45 mg

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

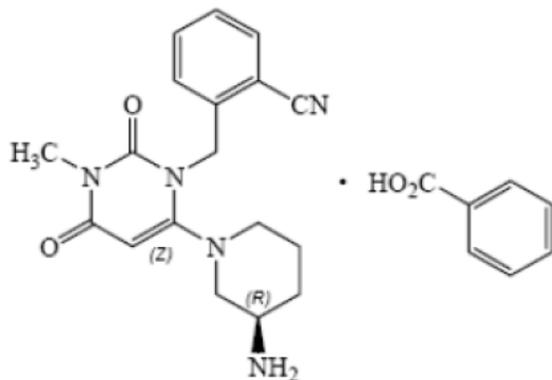
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

**a. Alogliptin Benzoate**Chemical Name(s):

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

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

Structural Formula (absolute stereochemistry):

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:

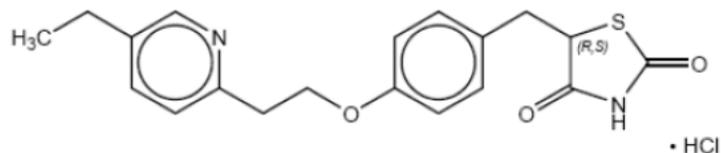
461.51 (benzoate salt)

339.39 (free base)

**b. Pioglitazone Hydrochloride**Chemical Name(s):

(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

## Chemistry Review Data Sheet

Structural Formula:Molecular Formula: C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S • HClMolecular Weight:

392.90 (HCl salt)

356.43 (free base)

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

| DMF #   | TYPE | HOLDER  | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) | III  | (b) (4) | (b) (4)         | 4                 | Adequate            |                       |          |
|         | III  |         |                 | 3                 | Adequate            | 12/07/2004            |          |
|         | III  |         |                 | 4                 | Adequate            |                       |          |
|         | III  |         |                 | 3                 | Adequate            | 10/16/2007            |          |
|         | III  |         |                 | 4                 | Adequate            | 3/11/2005             |          |
|         | III  |         |                 | 3                 | Adequate            | 12/22/2008            |          |
|         | III  |         |                 | 3                 | Adequate            | 6/20/2006             |          |
|         | III  |         |                 | 4                 | Adequate            | 11/19/2007            |          |
|         | III  |         |                 | 3                 | Adequate            | 8/4/2008              |          |

<sup>1</sup> Action codes for DMF Table:

Chemistry Review Data Sheet

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  |
|----------|--------------------|--|
| NDA      | 22-271             | Nesina® (Alogliptin); referenced for drug substance  |
| NDA      | 21-073             | Actos® (Pioglitazone); referenced for drug substance |

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION  | DATE | REVIEWER             |
|-------------------------------|---|------|----------------------|
| Biometrics                    |   |      |                      |
| EES                           | pending   |      | Office of Compliance |
| Pharm/Tox                     |   |      |                      |
| Biopharm                      | Pending, comments to Applicant attached at the end of this review |      | Tapash Ghosh         |
| LNC                           |   |      |                      |
| Methods Validation            |   |      |                      |
| OSE                           |   |      |                      |
| EA                            |   |      | Theodore Carver      |
| Microbiology                  |   |      |                      |

# The Chemistry Review for NDA 22-426

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC recommendation is pending the overall recommendation from the Office of Compliance (completion of establishment inspections) and the Applicant's response to the CMC IR letter.

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

A standard stability agreement is made. The applicant has agreed to complete 36-month long-term, intermediate and 6-month accelerated stability studies for 3 commercial lots of the drug product; in addition, the applicant agrees to add one commercial lot to the stability program each year following approval.

### II. Summary of Chemistry Assessments

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

##### Drug Substance:

All chemistry, manufacturing and controls information for each drug substance is contained in NDA 22-271 for alogliptin benzoate and NDA 21-073 for pioglitazone hydrochloride. NDA 22-271, for the single-entity alogliptin tablet, is currently under review, but has been recommended for approval by CMC and all outstanding CMC issues have been resolved.

Alogliptin benzoate is a new molecular entity not yet approved as a single entity tablet.

Alogliptin benzoate is a white to off-white crystalline powder, melting at 182.5°C, that is sparingly to moderately soluble over a wide range of pH (21.3 mg/mL at pH 7.0). The API has a single chiral center and is prepared as the R-enantiomer. The manufacturer for alogliptin benzoate is (b) (4). The manufacturing process for alogliptin benzoate is (b) (4).

The proposed release specifications include appearance, identification (IR and UV), heavy metals, (b) (4) water content, assay, related substance, residual solvents, and particle size. Clarification has been requested from the applicant regarding the proposed particle size specification, in light of API batch data. No other issues have been identified that will affect the use of this API in the proposed fixed-dose combination product. Although NDA

## Executive Summary Section

22-271 has been recommended for approval by CMC, CMC issues that may arise in either the single-entity or fixed dose combination product applications should be monitored as review of both applications continues.

Pioglitazone HCl is an approved drug in single-entity tablets, approved in 1999. Pioglitazone HCl is a white crystalline product that is sparingly soluble to practically insoluble above pH 2.0 (0.00093 mg/mL at pH 7.0). The API is a racemic mixture. Manufacture is by (b) (4)

The structure has been suitably characterized by elemental analysis, UV and IR spectroscopy, NMR spectroscopy ( $^1\text{H}$  and  $^{13}\text{C}$ ), and mass spectrometry. The pioglitazone HCl drug substance is well characterized with a 10-year manufacturing history since approval. The in-process controls and impurities profiles are well-defined and there is no history of significant issues with the manufacturing process. NDA 21-073 is an approved NDA for the Actos® marketed single-entity pioglitazone hydrochloride drug product.

**Drug Product:**

Alogliptin/pioglitazone is a fixed-dose combination oral product composed of two active ingredients, alogliptin benzoate and pioglitazone hydrochloride, formulated as (b) (4) film-coated, immediate-release tablets. The proposed drug product is intended to provide a single tablet with a clinical effect bioequivalent to the administration of two single-entity immediate release tablets each containing the same doses of the respective drugs. (b) (4)

The dose strengths in the fixed-dose combination product are 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone. The maximum daily dose is 25 mg alogliptin (free base)/45 mg pioglitazone (free base).

The proposed dosage forms and strengths are:

- 25 mg/15 mg tablets are yellow, round, biconvex, film-coated tablets, with both “A/P” and “25/15” printed on one side.
- 25 mg/30 mg tablets are peach, round, biconvex, film-coated tablets, with both “A/P” and “25/30” printed on one side.
- 25 mg/45 mg tablets are red, round, biconvex, film-coated tablets, with both “A/P” and “25/45” printed on one side.
- 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.

## Executive Summary Section

- 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.
- 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.

The excipients are mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hypromellose (b) (4), polyethylene glycol (b) (4), titanium dioxide, talc, ferric oxide (yellow and/or red), and printing ink (Red A1 or Gray F1). The proposed release specifications include appearance, identification (UV and HPLC), assay (HPLC), dissolution, and content uniformity. The applicant will be requested to include a related substances assay (HPLC) in the release specification. The proposed regulatory methods have been validated.

6 months long-term and 6 months accelerated stability data have been supplied in the original NDA submission. Applicant has requested 24 months shelf life, but only 12 months can be granted based upon the ICH Q1E guideline. Applicant obtained agreement from the FDA to submit 12 months long term stability data no later than 3 months prior to the PDUFA goal date for this application.

**B. Description of how the drug product is intended to be used**

(b) (4) (alogliptin/pioglitazone) is a fixed dose combination product consisting of two anti-diabetic drugs that function according to different mechanisms. Pioglitazone HCl belongs to the thiazolidinedione class of drugs, which activate peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) receptors. PPAR $\gamma$  receptors regulate the transcription of genes linked to insulin activation; therefore, activation of these receptors in target tissues effectively bypasses the defective insulin signaling resulting from insulin resistance. Alogliptin benzoate is a dipeptidyl peptidase IV inhibitor. DPP-IV rapidly degrades incretins, such as GLP-1 and GIP. Since incretin levels are lower in diabetic patients, artificially increasing their levels by inhibiting DPP-IV improves glycemic control by elevating insulin levels and reducing glucagon levels. Thus, whereas pioglitazone improves glycemic control intracellularly by bypassing insulin signaling in diabetic patients, the other drug improves glycemic control extracellularly by increasing the signaling due to insulin and other hormones involved in glycemic control. Patients whose diabetes is not adequately controlled by either drug alone may benefit from taking both drugs in combination, since they operate by different mechanisms. By providing six different dosage strengths of both drugs, the fixed dose combination product facilitates management of Type II diabetes with a single tablet in patients that benefit from receiving both drugs. The maximum daily dose is 25/45 mg/mg (free base/free base) alogliptin/pioglitazone. Bioequivalence studies were conducted with the highest and lowest strengths, 12.5/15 and 25/45. A biowaiver request is made for the other strengths.

Tablets of the drug product are provided in both professional samples and commercial package configurations. 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.

## Executive Summary Section

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

The CMC recommendation is pending the overall recommendation from the Office of Compliance (completion of establishment inspections) and the Applicant's response to the CMC IR letter.

**III. Administrative****A. Reviewer's Signature**

\_\_\_\_\_  
Theodore Carver, CMC Reviewer, ONDQA/PMA Division I

**B. Endorsement Block**

T. Carver/CMC Reviewer, 03/28/09  
A. Al-Hakim/Team Leader, 03/28/09

**C. CC Block**

Suong Tran/PAL, 03/28/09  
Julie Marchick/RPM, 03/28/09

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Theodore Carver  
3/30/2009 11:03:49 AM  
CHEMIST

Ali Al-Hakim  
3/30/2009 11:06:01 AM  
CHEMIST

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Division of Metabolism and Endocrinology Products**

**NDA:** 22-426

**Applicant:** Takeda Global Research & Development

**Stamp Date:** 22-SEP-2008

**PDUFA Date:** 22-JUL-2009

**Proposed Proprietary Name:** [none]

**Established Name:** Alogliptin/pioglitazone

**Dosage form and strength:** Immediate release tablet –  
25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45  
mg

**Route of Administration:** oral

**Indications:** Treatment of type 2 diabetes

**PAL:** Su (Suong) Tran, Branch II/DPA I/ONDQA

**ONDQA Fileability:** Yes

**Comments for 74-Day Letter:** Yes, on the last page.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

| CONSULTS/ CMC RELATED REVIEWS | COMMENT   |
|-------------------------------|---|
| Biopharmaceutics              | A consult review of the biowaiver request will be requested of the ONDQA Biopharmaceutics Review Staff. |
| CDRH or CBER                  | <i>Not Applicable</i>   |
| EA                            | Categorical exclusion request will be assessed by Primary Reviewer.                                     |
| EES                           | EER was sent to Office of Compliance on 08-OCT-2008.  |
| OSE                           | <i>Labeling consult request will be sent as part of DMEP's request.</i>                                 |
| Methods Validation            | <i>Validation may be requested of FDA labs after test methods are finalized.</i>                        |
| Microbiology                  | <i>Not Applicable</i>   |
| Pharm/Tox                     | <i>Not Applicable: No degradant exceeds (b) (4)</i>   |

**Summary: [See the discussion in Critical Issues later in this review.]**

This is an electronic NDA, filed as a 505(b)(1) application (reference is made to the pending NDA 22271 for alogliptin, which is a New Molecular Entity).

The product is a fixed dose combination, immediate-release (b) (4) tablet available in the strengths of 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone. Reference is made to NDA 22271 (currently under review by FDA) for the drug substance alogliptin benzoate and to the approved NDA 21073 for the drug substance pioglitazone hydrochloride. All three NDAs have the same applicant. The new fixed dose combination product combines the active ingredients of the referenced NDAs.

In support of efficacy, a pivotal bioequivalence (BE) study, Study 322OPI-101, was conducted to compare the combination tablet to the concomitantly administered individual products of NDA 22271 and NDA 21073 at the highest and lowest dosage strengths (12.5/15 and 25/45). A biowaiver request is made by the applicant for the other dosage strengths that were not included in the pivotal BE study.

**Maximum daily dose is 25/45 mg/mg (free base/free base) alogliptin/pioglitazone.**

|                                |  |
|--------------------------------|--|
| <b>Route of administration</b> | Oral   |
| <b>Dosage form</b>             | Immediate release tablet   |
| <b>Package type</b>            | For commercial distribution: HDPE bottle (b) (4) in 30-count (b) (4) 90-count (b) (4), and 500-count (b) (4)<br>For physicians' samples: 7-count HDPE bottle (b) (4) or 7-count (b) (4) blisters (b) (4) |
| <b>Potency</b>                 | 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone   |

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

|                      |  |
|----------------------|--|
| <b>Color</b>         | 25/15 mg/mg: yellow<br>25/30 mg/mg: peach<br>25/45 mg/mg: red<br>12.5/15 mg/mg: pale yellow<br>12.5/30 mg/mg: pale peach<br>12.5/45 mg/mg: pale red  |
| <b>Shape</b>         | Round.   |
| <b>Coating</b>       | Film coated.   |
| <b>Size</b>          | [unknown] <i>Comment for the 74-day letter.</i>  |
| <b>Scoring</b>       | None.  |
| <b>Imprint codes</b> | 25/15 mg/mg: (on the same side of tablet) A/P and 25/15<br>25/30 mg/mg: (on the same side of tablet) A/P and 25/30<br>25/45 mg/mg: (on the same side of tablet) A/P and 25/45<br>12.5/15 mg/mg: (on the same side of tablet) A/P and 12.5/15<br>12.5/30 mg/mg: (on the same side of tablet) A/P and 12.5/30<br>12.5/45 mg/mg: (on the same side of tablet) A/P and 12.5/45 |
| <b>Symbols</b>       | None.  |

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Drug substance:**

**[See the discussion in Critical Issues later in this review.]**

**Alogliptin benzoate**

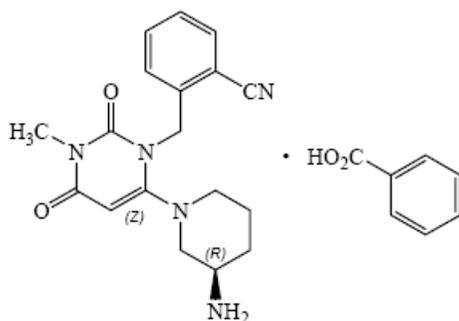
Alogliptin is a potent, selective, orally bioavailable inhibitor of the enzymatic activity of DPP-4.

**Chemical Names:**

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

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

**Figure 2.a Structural Formula of Alogliptin Benzoate (Absolute Stereochemistry)**



**Molecular Formula:**

$C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$

**Molecular Weight:**

461.51 (benzoate salt)

339.39 (free base)

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Table 3.a Summary of General Properties for Alogliptin Benzoate**

| Property   | Result  |              |                         |
|--|---|--------------|-------------------------|
| Appearance   | White crystalline powder  |              |                         |
| Odor   | Odorless  |              |                         |
| Melting point  | 182.5°C   |              |                         |
| Dissociation constant (pK <sub>a</sub> )                                       | 8.5   |              |                         |
| Specific rotation [ $\alpha$ ] <sub>D</sub> <sup>20</sup>                      | +16° in dimethylsulfoxide   |              |                         |
| Hygroscopicity   | Non-hygroscopic   |              |                         |
| Solubility profile in organic solvents at 25°C (a)                             | Dimethylsulfoxide   | 92.7 mg/mL   | (soluble)               |
|  | Methanol  | 28.6 mg/mL   | (sparingly soluble)     |
|  | Tetrahydrofuran   | 4.2 mg/mL    | (slightly soluble)      |
|  | Ethanol   | 4.1 mg/mL    | (slightly soluble)      |
|  | Acetonitrile  | 1.5 mg/mL    | (slightly soluble)      |
|  | Isopropyl alcohol   | 1.2 mg/mL    | (slightly soluble)      |
|  | 1-Octanol   | 0.6 mg/mL    | (very slightly soluble) |
|  | Isopropyl acetate   | 0.4 mg/mL    | (very slightly soluble) |
|  | Diethyl ether   | 0.07 mg/mL   | (Practically insoluble) |
|  | Toluene   | 0.05 mg/mL   | (Practically insoluble) |
| Solubility profile in aqueous solution at 25°C (a)                             | Water   | 19.2 mg/mL   | (sparingly soluble)     |
|  | 0.1 mol/L HCl   | 51.9 mg/mL   | (soluble)               |
|  | 0.1 mol/L NaOH  | 49.6 mg/mL   | (soluble)               |
|  | pH 3.0 (b)  | 26.1 mg/mL   | (sparingly soluble)     |
|  | pH 5.0 (b)  | 21.8 mg/mL   | (sparingly soluble)     |
|  | pH 7.0 (b)  | 21.3 mg/mL   | (sparingly soluble)     |
|  | pH 9.0 (b)  | 23.2 mg/mL   | (sparingly soluble)     |
|  | pH 11.0 (b)   | 27.3 mg/mL   | (sparingly soluble)     |
| Solubility profile in aqueous solution at 37°C (c)                             | 0.1 mol/L HCl, pH 1.0   | 47.0 mg/mL   | (highly soluble)        |
|  | 0.01 mol/L HCl, pH 2.0  | 27.1 mg/mL   | (highly soluble)        |
|  | Acetate buffer, pH 4.5  | 27.6 mg/mL   | (highly soluble)        |
|  | Phosphate buffer, pH 6.8  | 21.9 mg/mL   | (highly soluble)        |
|  | Phosphate buffer, pH 7.5  | 23.6 mg/mL   | (highly soluble)        |
| Partition coefficients (C <sub>1-octanol</sub> /C <sub>aqueous</sub> ) at 25°C | <u>Buffer pH (b)</u>  | <u>Log P</u> |                         |
|  | 3.0   | -4.8         |                         |
|  | 4.0   | -3.8         |                         |
|  | 5.0   | -2.8         |                         |
|  | 6.0   | -1.9         |                         |
|  | 6.5   | -1.4         |                         |
|  | 7.0   | -0.9         |                         |
|  | 7.4   | -0.5         |                         |
|  | 8.0   | 0.0          |                         |
|  | 9.0   | 0.5          |                         |
|  | 10.0  | 0.6          |                         |
|  | 11.0  | 0.6          |                         |
| 12.0   | 0.6   |              |                         |
| Polymorphism   | No evidence of polymorphism   |              |                         |
| Chiral centers   | One chiral center located at the 3-position of the aminopiperidine moiety |              |                         |

Footnotes for Table 3.a on the following page

Footnotes for Table 3.a

(a) Description according to EP and USP definitions of solubility.

(b) Britton Robinson's buffer (J. Chem. Soc., 1456-1462, Vol. I (1931)).

(c) Highly soluble as defined by BCS solubility class 1 according to FDA guidance "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Bioequivalence Classification System," August 2000, and by EMEA guidance "Note for Guidance on the Investigation of Bioavailability and Bioequivalence," 2001, using a maximum daily dose of 25 mg.

There is no chemistry, manufacturing, and controls information on alogliptin benzoate in the NDA.

Reference is made to NDA 22271 submitted by the same applicant and currently under review by FDA.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Pioglitazone hydrochloride**

Pioglitazone is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance.

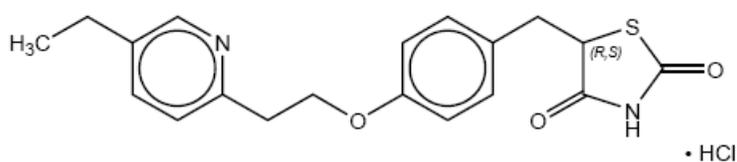
**Chemical Names:**

(±)-5-[[4-[2-(5-Ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monhydrochloride

(±)-5-[*p*-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride

(±)-5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione monhydrochloride

**Figure 2.a Structural Formula of Pioglitazone Hydrochloride**



**Molecular Formula:**

$C_{19}H_{20}N_2O_3S \cdot HCl$

**Molecular Weight:**

392.90

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Table 3.a Summary of General Properties for Pioglitazone Hydrochloride**

| Property   | Result                       |          |                       |
|--|------------------------------|----------|-----------------------|
| Description  | White crystalline powder     |          |                       |
| Odor   | Odorless                     |          |                       |
| Melting point  | 193°C with decomposition     |          |                       |
| Specific rotation $[\alpha]_D^{20}$<br>Pioglitazone HCl                            | 0.0° (in dimethylformamide)  |          |                       |
| Individual Isomers   |                              |          |                       |
| (+)-Pioglitazone HCl   | +134° (in dimethylformamide) |          |                       |
| (-)-Pioglitazone HCl   | -137° (in dimethylformamide) |          |                       |
| Solubility Profile (in mg/mL) in<br>Organic Solvents at 20°C (a)                   |                              |          |                       |
|  | Dimethylsulfoxide            | 335      | freely soluble        |
|  | Dimethylformamide            | 88       | soluble               |
|  | Methanol                     | 79       | soluble               |
|  | Glacial Acetic Acid          | 11       | sparingly soluble     |
|  | Ethanol                      | 8.1      | slightly soluble      |
|  | Chloroform                   | 3.4      | slightly soluble      |
|  | Acetonitrile                 | 0.84     | very slightly soluble |
|  | Acetone                      | 0.49     | very slightly soluble |
|  | Acetic Anhydride             | 0.48     | very slightly soluble |
|  | Octanol                      | 0.30     | very slightly soluble |
|  | Diethyl Ether                | 0.0051   | insoluble             |
|  | <i>n</i> -Hexane             | 0.000055 | insoluble             |
| Solubility Profile (in mg/mL) in<br>Aqueous Solutions of Various pH<br>at 20°C (a) |                              |          |                       |
|  | Water                        | 0.032    | practically insoluble |
|  | pH 1.1; 0.1N HCl             | 6.7      | slightly soluble      |
|  | pH 2.0 (b)                   | 0.42     | very slightly soluble |
|  | pH 3.3 (b)                   | 0.014    | practically insoluble |
|  | pH 5.0 (b)                   | 0.00026  | insoluble             |
|  | pH 7.0 (b)                   | 0.000093 | insoluble             |
|  | pH 9.1 (b)                   | 0.010    | practically insoluble |
|  | pH 11.1 (b)                  | 0.13     | very slightly soluble |
|  | pH 13.0; 0.1N NaOH           | 17       | sparingly soluble     |
| Partition Coefficients at 20°C<br>[C1-octanol/ Aqueous]                            | Aqueous layer                |          |                       |
|  | pH 1.0; 0.1N HCl             | 0.4      |                       |
|  | pH 3.0 (b)                   | 85       |                       |
|  | pH 5.0 (b)                   | >1000    |                       |
|  | pH 6.0 (b)                   | >1000    |                       |
|  | pH 7.0 (b)                   | >1000    |                       |
|  | pH 8.0 (b)                   | 342      |                       |
|  | pH 9.0 (b)                   | 46       |                       |
|  | pH 9.9 (b)                   | 11       |                       |
| Physical Form  | No evidence of polymorphism  |          |                       |

(a) Descriptive terms according to USP definitions of solubility.

(b) Britton Robinson's Buffer Solution.

There is no chemistry, manufacturing, and controls information on pioglitazone HCl in the NDA. Reference is made to the approved NDA 21073 submitted by the same applicant.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Drug product:**

**[See the discussion in Critical Issues later in this review.]**

The product is a fixed dose combination, immediate-release (b) (4) tablet available in the strengths of 25/15, 25/30, 25/45, 12.5/15, 12.5/30, and 12.5/45 mg/mg (free base/free base) alogliptin/pioglitazone.



**Figure 6** Cross Section of SYR-322-4833 (b) (4) Tablets

See the composition on the next pages.

The manufacture of the tablets consists of (b) (4)  
(b) (4)  
(b) (4)

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Table 2.a      Composition of SYR-322-4833 Tablets, 12.5mg+15mg, 12.5mg+30mg, and 12.5mg+45mg**

| Component  | Reference to Quality Standards | Function          | Quantity per Tablet (mg) |               |               |         |
|--|--------------------------------|-------------------|--------------------------|---------------|---------------|---------|
|  |                                |                   | 12.5mg +15mg             | 12.5mg +30mg  | 12.5mg +45mg  |         |
| Alogliptin benzoate (1)<br>(As the free base)        | In-house                       | Active ingredient | 17<br>(12.5)             | 17<br>(12.5)  | 17<br>(12.5)  | (b) (4) |
| Mannitol   | Ph.Eur., USP                   |                   |                          |               |               | (b) (4) |
| Cellulose, microcrystalline                          | Ph.Eur., NF                    |                   |                          |               |               |         |
| Hydroxypropylcellulose                               | Ph.Eur., NF                    |                   |                          |               |               |         |
| Croscarmellose sodium                                | Ph.Eur., NF                    |                   |                          |               |               |         |
| Magnesium stearate                                   | Ph.Eur., NF                    |                   |                          |               |               |         |
| (b) (4)  |                                |                   |                          |               |               |         |
| Pioglitazone hydrochloride (3)<br>(As the free base) | In-house                       | Active ingredient | 16.53<br>(15)            | 33.06<br>(30) | 49.59<br>(45) | (b) (4) |
| Lactose monohydrate                                  | Ph.Eur., NF                    |                   |                          |               |               | (b) (4) |
| (b) (4)  |                                |                   |                          |               |               |         |
| <b>Film-Coating</b> (b) (4)                          |                                |                   |                          |               |               |         |
| Hypromellose (b) (4)                                 | Ph.Eur., USP                   |                   |                          |               |               | (b) (4) |
| Talc   | Ph.Eur., USP                   |                   |                          |               |               |         |
| Titanium dioxide                                     | Ph.Eur., USP                   |                   |                          |               |               |         |
| Iron oxide yellow (b) (4)                            | 95/45/EC, NF                   |                   |                          |               |               |         |
| Iron oxide red (b) (4)                               | 95/45/EC, NF                   |                   |                          |               |               |         |
| (b) (4)  |                                |                   |                          |               |               |         |
| <b>Printing Ink</b> (b) (4)                          |                                |                   |                          |               |               |         |
| Printing ink Red A1 (5)                              | Manufacturer's standard        |                   |                          |               |               | (b) (4) |
| (b) (4)  |                                |                   |                          |               |               |         |

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Table 2.b Composition of SYR-322-4833 Tablets, 25mg+15mg, 25mg+30mg, and 25mg+45mg**

| Component  | Reference to Quality Standards | Function          | Quantity per Tablet (mg) |               |               |         |
|--|--------------------------------|-------------------|--------------------------|---------------|---------------|---------|
|  |                                |                   | 25mg +15mg               | 25mg +30mg    | 25mg +45mg    |         |
| Alogliptin benzoate (1)<br>(As the free base)        | In-house                       | Active ingredient | 34<br>(25)               | 34<br>(25)    | 34<br>(25)    | (b) (4) |
| Mannitol   | Ph.Eur., USP                   |                   |                          |               |               | (b) (4) |
| Cellulose, microcrystalline                          | Ph.Eur., NF                    |                   |                          |               |               | (b) (4) |
| Hydroxypropylcellulose                               | Ph.Eur., NF                    |                   |                          |               |               | (b) (4) |
| Croscarmellose sodium                                | Ph.Eur., NF                    |                   |                          |               |               | (b) (4) |
| Magnesium stearate                                   | Ph.Eur., NF                    |                   |                          |               |               | (b) (4) |
| Pioglitazone hydrochloride (3)<br>(As the free base) | In-house                       | Active ingredient | 16.53<br>(15)            | 33.06<br>(30) | 49.59<br>(45) | (b) (4) |
| Lactose monohydrate                                  | Ph.Eur., NF                    |                   |                          |               |               | (b) (4) |
| <b>Film-Coating</b>                                  |                                |                   |                          |               |               | (b) (4) |
| Hypromellose (b) (4)                                 | Ph.Eur., USP                   |                   |                          |               |               | (b) (4) |
| Talc   | Ph.Eur., USP                   |                   |                          |               |               | (b) (4) |
| Titanium dioxide                                     | Ph.Eur., USP                   |                   |                          |               |               | (b) (4) |
| Iron oxide yellow (b) (4)                            | 95/45/EC, NF                   |                   |                          |               |               | (b) (4) |
| Iron oxide red (b) (4)                               | 95/45/EC, NF                   |                   |                          |               |               | (b) (4) |
| <b>Printing Ink</b>                                  |                                |                   |                          |               |               | (b) (4) |
| Printing ink Gray F1 (5)                             | Manufacturer's standard        |                   |                          |               |               | (b) (4) |

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Table 1.a Specifications of SYR-322-4833 Tablets (12.5mg+15mg, 12.5mg+30mg, 12.5mg+45mg, 25mg+15mg, 25mg+30mg, and 25mg+45mg)**

| Test Item               | Acceptance criteria   | Analytical procedure                 |  |
|-------------------------|---|--------------------------------------|--|
| Appearance              | Round, biconvex, film-coated tablet.  | <a href="#">SYR-322-4833/ 00084</a>  |  |
|                         | <i>Strength</i> <i>Color</i> <i>Printing (1 side)</i>                               |                                      |  |
|                         | 12.5 mg+15 mg   | Pale yellow      "A/P" and "12.5/15" |  |
|                         | 12.5 mg+30 mg   | Pale peach      "A/P" and "12.5/30"  |  |
|                         | 12.5 mg+45 mg   | Pale red      "A/P" and "12.5/45"    |  |
|                         | 25 mg+15 mg   | Yellow      "A/P" and "25/15"        |  |
|                         | 25 mg+30 mg   | Peach      "A/P" and "25/30"         |  |
|                         | 25 mg+45 mg   | Red      "A/P" and "25/45"           |  |
| Identification          | (b) (4)   |                                      |  |
| A. Ultraviolet Spectrum |   | <a href="#">SYR-322-4833/ 00085</a>  |  |
| Alogliptin              |   |                                      |  |
| Pioglitazone            |   |                                      |  |
| B. HPLC Retention Time  |   | <a href="#">SYR-322-4833/ 00086</a>  |  |
| Assay (%)               |   | <a href="#">SYR-322-4833/ 00088</a>  |  |
| Alogliptin              |   |                                      |  |
| Pioglitazone            |   |                                      |  |
| Dissolution (%)         |   | <a href="#">SYR-322-4833/ 00089</a>  |  |
| Alogliptin              |   |                                      |  |
| Pioglitazone            |   |                                      |  |
| Content Uniformity (%)  |   | <a href="#">SYR-322-4833/ 00087</a>  |  |
| Alogliptin              | Meets the requirements of USP <905>, Uniformity of Dosage Units, Content Uniformity |                                      |  |
| Pioglitazone            | Meets the requirements of USP <905>, Uniformity of Dosage Units, Content Uniformity |                                      |  |

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

The proposed commercial packaging configurations for all strengths of SYR-322-4833 Tablets include high density polyethylene (HDPE) bottles (b) (4) and (b) (4) blisters as listed in Table 3.a.

**Table 3.a Proposed Commercial Packaging Configurations for SYR-322-4833 Tablets**

| Configuration  | Container/Closure Components   |
|--|--------------------------------|
| Bottle of 7 tablets for physician samples                  | (b) (4) HDPE bottle<br>(b) (4) |
| Bottle of 30 tablets                                       | (b) (4) HDPE bottle<br>(b) (4) |
| Bottle of 90 tablets                                       | (b) (4) HDPE bottle<br>(b) (4) |
| Bottle of 500 tablets                                      | (b) (4) HDPE bottle<br>(b) (4) |
| (b) (4) blister package of 7 tablets for physician samples | (b) (4) foil<br>(b) (4)        |

The drug product is stored at (b) (4) 25 °C. See the discussion on stability data under Critical Issues.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Relevant batches of drug product:**



See Discussion under Critical Issues.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**CRITICAL ISSUES**

- **Has all information requested during the IND phases, and at the pre-NDA meetings been included?** Yes. The NDA includes some information as requested by FDA during the IND development. However, there is no direct item-by-item response to FDA's questions, which makes it difficult to assess, for the purpose of this filing memo/IQA, whether the applicant has provided a satisfactory response to each question. The primary reviewer will assess the information in the NDA and decide whether each question has been satisfactorily addressed.

The following are previous comments sent to the applicant:

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

Chemistry, Manufacturing, and Controls

1. Does the FDA agree that this stability strategy is sufficient to support the filing of all 6 strengths of the SYR-322-4833 FDC drug product? Does the FDA also agree that the reduced study design can be utilized to fulfill the post approval stability commitment for the first 3 commercial scale lots of each strength placed on stability?

**Division Response:** Your proposal to submit only 6 months of stability data from the long-term storage condition together with 6 months stability data from accelerated conditions and a commitment to provide 12 months of long-term results no later than 3 months prior to the PDUFA goal date would not preclude filing of the planned original NDA for all 6 strengths of SYR-322-4833 FDC drug product.

Your proposed (b) (4) stability study design (b) (4) is acceptable.

However, we strongly recommend that you submit a complete stability package in the original NDA, including at least 12 months of long term data. While every effort will be made to review amendments containing stability updates, the review of such amendments will depend on the timeliness of submission, extent of submitted data, and

available resources. Therefore, in accordance with Good Review Management Principles and Practice (GRMP) timelines, we cannot guarantee that we will be able to review such amendments late in the review cycle.

The shelf life for the product will be based on the long-term and accelerated stability data that is submitted and reviewed. Under certain circumstances, extrapolation of the shelf life beyond the period covered by the long-term data can be appropriate (see ICH Guidance for Industry: Q1E Evaluation of Stability Data).

We recommend that you provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage condition and container closure system. We also recommend that you provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.

You may propose in the NDA a desired shelf life for the products. However, the final determination of the actual shelf life will be a NDA review issue.

2. Does the FDA agree that this strategy for addressing process validation is sufficient to support the commercialization of all 6 strengths of the SYR-322-4833 FDC drug product?

**Division Response:** Your proposed process validation strategy is considered a Current Good Manufacturing Practices (CGMP) matter, therefore your question has been forwarded to the Center for Drug Evaluation and Research (CDER) Office of Compliance for response. We will respond to this question in a separate correspondence.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

3. Does the FDA agree that 6 months of stability results at long-term and accelerated conditions and including commitments to provide 12 months of long-term results no later than 3 months prior to the PDUFA goal date is sufficient to successfully file the SYR-322-4833 fixed-dose combination products?

**Response: The NDA may be submitted with 6 months stability data and stability updates may be submitted in a timely manner. While every effort will be made to review the stability updates, their review will depend on the timeliness of submission, extent of submitted data, and available resources. The expiration data period will be commensurate with the submitted stability data.**

**CRITICAL ISSUES (continued)**

- The primary reviewer will assess the information in the NDA and decide whether comments previously conveyed to the sponsor have been satisfactorily addressed.
- **Drug substance.** Reference is made to NDA 22271 (currently under review by FDA) for the drug substance alogliptin benzoate and to the approved NDA 21073 for the drug substance pioglitazone hydrochloride. All three NDAs have the same applicant. The reviewer will document the current chemistry recommendation on each drug substance and any information on either that may be of use in the review of the fixed dose combination product.
- **Dosage strength.** The dosage strengths are based on the established names of the drug substances, alogliptin and pioglitazone. 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. The reviewer will confirm that the product labeling correctly reflects the free-base and salt amounts.
- **Differences between the clinical/stability batches and the commercial product.** The applicant states that the composition of the (b) (4) tablets used in the pivotal BE studies is the same as that of the commercial (b) (4) tablets. This final formulation is called (b) (4) to distinguish from an earlier unsuccessful formulation called (b) (4). The registration batches (stability and pivotal BE batches) were manufactured at pilot-scale (b) (4) using the identical process for the commercial product (b) (4) at the same manufacturing campus, and using the same or

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

equivalent equipment. The reviewer will confirm that there is no significant difference in the manufacturing of the registration batches and the commercial product. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- **Manufacturing process.** The manufacture of the tablets consists of [REDACTED] (b) (4)

[REDACTED]

- **Product specification.** The drug product specification lacks testing for related substances, microbial content, [REDACTED] (b) (4) and hardness. The reviewer will evaluate the applicant’s justification of the proposed specification and determine whether the lack of testing for related substances [REDACTED] (b) (4) [REDACTED] can be allowed.

- The applicant states that no impurity/degradant has been found above the level of [REDACTED] (b) (4). The reviewer will evaluate the adequacy of the test method used to test for impurities/degradants in order to “qualify” the claim that there is none above [REDACTED] (b) (4). The stability protocols for the primary stability batches and future commercial batches do include Related Substances testing, but for information purposes only. The reviewer will decide whether this testing should have acceptance criteria (i.e., be part of the specification) until sufficient data can be evaluated in support of the elimination of this test from the specification.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

- [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED] The reviewer will assess [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] in ensuring product integrity during storage.
- **Stability of the drug product.** As agreed by FDA in the Pre-NDA meeting minutes, the NDA is filed with 6-month stability data for the primary stability batches, with the applicant’s commitment to provide 12-month data “no later than 3 months prior to the PDUFA goal”. [It should be noted that this pre-NDA agreement was made prior to CDER’s current policy that no agreement should be made for amendments to be submitted during the review cycle because a complete NDA should be submitted for filing as per GRMPs.] The primary stability batches are three pilot-scale batches of each strength packaged in the proposed commercial container closure systems. [REDACTED] (b) (4)  
[REDACTED] The primary reviewer will evaluate any trending and determine an expiry as per ICH Q1E, based on all available data that best represent the commercial product’s stability profile.
- **Container closure components.** Reviews of the packaging DMFs may not be necessary if the reviewer finds the information included in the NDA on the safety and suitability of the product-contact components adequate as per CDER’s current policy on packaging components for a solid oral dosage product. In the 74-day letter, the applicant will be asked to provide references to the 21 CFR [REDACTED] (b) (4) regulations for the [REDACTED] (b) (4) container closure systems.
- **Biopharmaceutics.** No IVIVC is claimed by the applicant. In support of efficacy, a pivotal bioequivalence (BE) study, Study 322OPI-101, was conducted to compare the combination tablet to the concomitantly administered individual products of NDA 22271 and NDA 21073 at the highest and lowest dosage strengths (12.5/15 and 25/45). A biowaiver request is made by the applicant for the other dosage strengths that were not included in the pivotal BE study. A consult review of the biowaiver request will be requested of the ONDQA Biopharmaceutics Review Staff.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Supporting NDA or IND:**

IND 73193, IND 69707, NDA 22271, NDA 21073

**Supporting DMF:**

A listing of Drug Master Files (DMF) cross-referenced in NDA 22-426, alogliptin/pioglitazone fixed dose combination tablets and the corresponding letters of authorization are provided in this application.

| DMF<br>Number | Item | Company/Address |
|---------------|------|-----------------|
|               |      |                 |

(b) (4)

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**GMP facilities: EER was sent to the Office of Compliance on 08-OCT-2008. As per Compliance's email (attached), the facilities manufacturing intermediates were cancelled from the EER.**

**From:** Adams, Shawnte L  
**Sent:** Wednesday, October 08, 2008 12:07 PM  
**To:** Marchick, Julie; Tran, Suong T  
**Cc:** Charity, Anthony  
**Subject:** NDA 22426

Please provide a justification for the need to inspect the intermediate manufacturers submitted in NDA 22426. Is there some critical aspect that is not verified or qualified at the drug substance manufacturer that would require an inspection to occur at any of the intermediate manufacturers? It is not our policy to inspect intermediate manufacturers without a specific reason or justification. If there is no critical need to inspect these facilities please cancel the request for the associated EERs.

Thank you,

Shawnte L. Adams  
Program Analyst  
Office of Compliance  
Division of Manufacturing and Product Quality  
International Compliance Team  
301-796-3193 (Office)  
301-847-8738 (Fax)

General Foreign Inspection questions should be directed to: [cderict@fda.hhs.gov](mailto:cderict@fda.hhs.gov)

FWAP: Tuesday and Thursday

*Lead by the power of your example rather than by the example of your power*

Alogliptin benzoate drug substance will be manufactured and released for commercial products at the following facility:



Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

Pioglitazone hydrochloride drug substance is manufactured for commercial product at the following facilities:

Takeda Pharmaceutical Company, Limited (TPC)  
Hikari Plant  
4720, Takeda Mitsui, Hikari  
Yamaguchi 743-8502, Japan

Contract Facilities



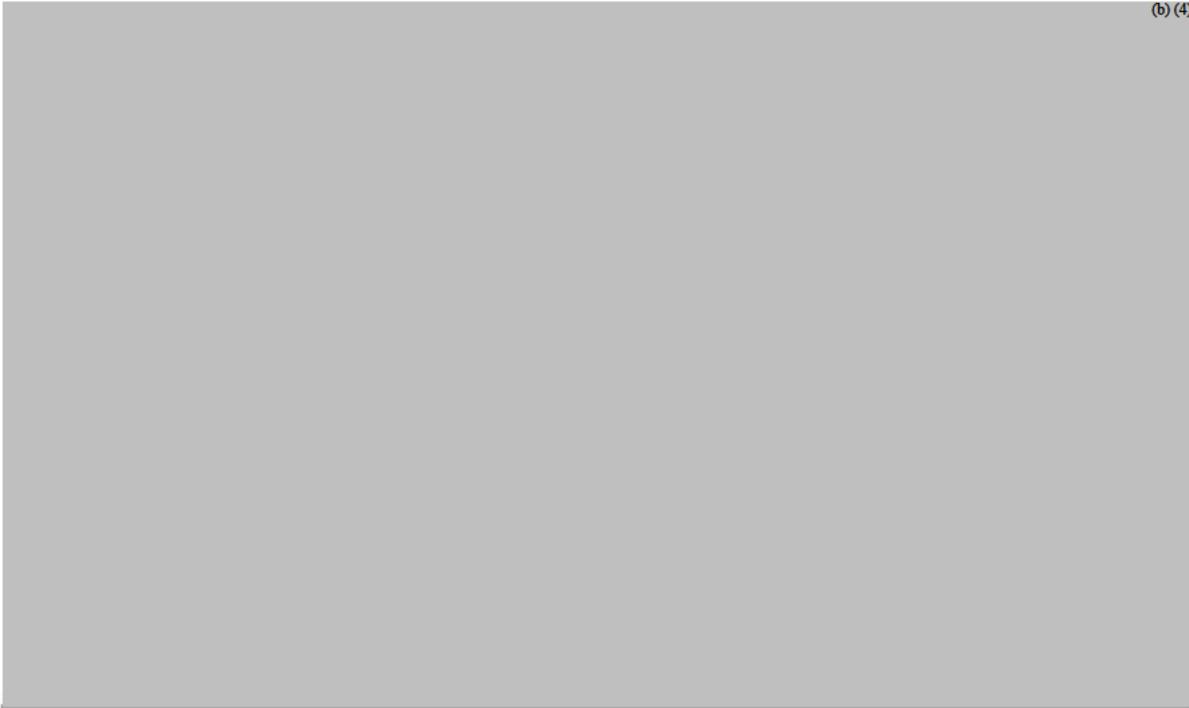
In addition, the key intermediate in the manufacture of pioglitazone hydrochloride, (b) (4) may be produced under contract at the following facilities:



Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

The firms listed below will perform the indicated functions in the commercial manufacture and control of SYR-322-4833 Tablets:

| <b>Firm</b>   | <b>Function</b>   |
|---|---|
| Takeda Pharmaceutical Company Limited<br>17-85, Juso-honmachi 2-chome, Yodogawa-ku<br>Osaka, 532-8686 Japan | Manufacture, testing and release, and packaging for<br>bulk shipment. |



(b) (4)

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**CHEMISTRY NDA FILING CHECKLIST**

**IS THE CMC SECTION OF APPLICATION FILEABLE? Yes**

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

|    | Content Parameter  | Yes | No | Comment   |
|----|--|-----|----|---|
| 1  | Is the section legible, organized, indexed, and paginated adequately?  | x   |    |   |
| 2  | Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)? | x   |    |   |
| 3  | Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?  |     | x  | Request for this statement will be part of the 74-day letter. |
| 4  | Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?   | x   |    |   |
| 5  | Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?   | x   |    |   |
| 6  | Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?  | x   |    |   |
| 7  | If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?                              | x   |    |   |
| 8  | Have draft container labels and package insert been provided?  | x   |    |   |
| 9  | Have all DMF References been identified?   | x   |    |   |
| 10 | Is information on the investigational formulations included?   | x   |    |   |
| 11 | Is information on the methods validation included?   | x   |    |   |
| 12 | If applicable, is documentation on the sterilization process validation included?  |     |    | Not applicable: oral dosage form.                             |

**74-Day Letter – Comments to the Applicant:**

1. Confirm that the manufacturing and testing facilities listed in the NDA Form 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and indicate whether each facility is ready for inspection or, if not, when it will be ready.
2. Provide the physical dimension of the finished tablet.
3.  (b) (4)
4. Provide a justification  (b) (4)
5.  (b) (4)
6. Provide references to the 21 CFR  (b) (4) regulations for the  (b) (4) container closure systems used to package the drug substance and drug product.

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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 Tran  
10/28/2008 02:50:06 PM  
CHEMIST

as we discussed.

Ali Al-Hakim  
10/28/2008 03:38:25 PM  
CHEMIST