CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022426Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **022426** SUPPL # **n/a** HFD # **n/a**

Trade Name **Oseni**

Generic Name **Alogliptin and pioglitazone fixed-dose combination tablets**

Applicant Name **Takeda Pharmaceuticals U.S.A., Inc.**

Approval Date, If Known **January 25, 2013**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Not specified

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **n/a**

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **021073** **Actos (pioglitazone) tablets**

NDA# **022271** **Nesina (alogliptin) tablets**

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

n/a

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

n/a

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

n/a

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

322OPI-002 – A multicenter, double blind study to determine the efficacy and safety of SYR-322 plus pioglitazone HCl, SYR-322 alone, or pioglitazone HCl alone in subjects with T2DM

322OPI-001 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of the combination of SYR-322 and pioglitazone in subjects with T2DM

322OPI-004 – A multicenter, randomized, double blind study to determine the efficacy and safety of the addition of SY-322 25 mg versus dose titration from 30 mg to 45 mg of pioglitazone HCl in subjects with T2DM who have inadequate control on a combination of metformin and 30 mg of pioglitazone HCl therapy

322-301 – A multicenter, randomized, double blind, placebo controlled, parallel group study comparing SYR-322 alone and combination SYR-322 with pioglitazone versus placebo on postprandial lipids in subjects with T2DM

322-009 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR-322 when used in combination with pioglitazone in subjects with T2DM

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1: **322OPI-002** YES ☐ NO ☒

Investigation #2: **322OPI-001** YES ☐ NO ☒

Investigation #3: **322OPI-004** YES ☐ NO ☒

Investigation #4: **322-301** YES ☐ NO ☒

Investigation #5: **322-009** YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

n/a

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1: **322OPI-002** YES ☐ NO ☒

Investigation #2: **322OPI-001** YES ☐ NO ☒

Investigation #3: **322OPI-004** YES ☐ NO ☒

Investigation #4: **322-301** YES ☐ NO ☒

Investigation #5: **322-009** YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

n/a

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

322OPI-002 – A multicenter, double blind study to determine the efficacy and safety of SYR-322 plus pioglitazone HCl, SYR-322 alone, or pioglitazone HCl alone in subjects with T2DM

322OPI-001 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of the combination of SYR-322 and pioglitazone in subjects with T2DM

322OPI-004 – A multicenter, randomized, double blind study to determine the efficacy and safety of the addition of SY-322 25 mg versus dose titration from 30 mg to 45 mg of pioglitazone HCl in subjects with T2DM who have inadequate control on a combination of metformin and 30 mg of pioglitazone HCl therapy

322-301 – A multicenter, randomized, double blind, placebo controlled, parallel group study comparing SYR-322 alone and combination SYR-322 with pioglitazone versus placebo on postprandial lipids in subjects with T2DM

322-009 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR-322 when used in combination with pioglitazone in subjects with T2DM

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1: **322OPI-002** !

IND # **073193** YES ☒ ! NO ☐
! Explain:

Investigation #2: **322OPI-001** !

IND # **073193** YES ☒ ! NO ☐
! Explain:

Investigation #3: **322OPI-004** !

IND # **073193** YES ☒ ! NO ☐
! Explain:

Investigation #4: **322-301** !

IND # **073193** YES ☒ ! NO ☐
! Explain:

Investigation #5: **322-009** !

IND # **073193** YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

Investigation #1 !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !

YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

n/a

==========

Name of person completing form: Richard Whitehead
Title: Regulatory Project Manager
Date: 1/24/13

Name of Office/Division Director signing form: Mary Parks, MD
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD E WHITEHEAD
01/29/2013

MARY H PARKS
01/29/2013

1.3.3 Debarment Certification

Certification Statement as requested by the Generic Drug Enforcement Act of 1992:

This certification is provided for New Drug Application (NDA 22-426, alogliptin/pioglitazone fixed dose combination tablet). Takeda Global Research & Development Center, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this application.

14-JUL-2011

Jeffrey Soderquist
Vice President, Quality Assurance
Takeda Global Research and Development Center, Inc.

Date

1.3.3 DEBARMENT CERTIFICATION

Certification Statement as requested by the Generic Drug Enforcement Act of 1992:

This certification statement is provided for New Drug Application (NDA 22-426, alogliptin/pioglitazone fixed dose combination tablets) and is provided in compliance with the Generic Drug Enforcement Act of 1992. Takeda Global Research & Development Center, Inc. hereby certifies it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

David Recker, MD, FACP, FACR
Senior Vice President, Clinical Sciences
Takeda Global Research & Development Center, Inc.

08-25-08
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **022426** BLA # **N/A**	NDA Supplement # **N/A** BLA STN # **N/A**	If NDA, Efficacy Supplement Type: **N/A**
Proprietary Name: **Oseni** Established/Proper Name: **alogliptin and pioglitazone** Dosage Form: **Tablets**		Applicant: **Takeda Pharmaceuticals, U.S.A., Inc.** Agent for Applicant (if applicable): **N/A**
RPM: **Richard Whitehead**		Division: **Metabolism and Endocrinology Products (DMEP)**

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

N/A

Provide a brief explanation of how this product is different from the listed drug.

N/A

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain) **N/A**

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check: **N/A**

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is **April 25, 2012**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	**CR – September 2, 2009**

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? **N/A** Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain **N/A**	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): **Type 1, 4**

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☒ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments: **None**

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) **N/A**	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* **N/A**	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # **N/A** and date exclusivity expires: **N/A**
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # **N/A** and date exclusivity expires: **N/A**
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # **N/A** and date exclusivity expires: **N/A**
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # **N/A** and date exclusivity expires: **N/A**
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # **N/A** and date 10-year limitation expires: **N/A**
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: N/A Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire **N/A**
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 4/21/11

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	☐ Yes ☐ No
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	**1-29-13**
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	**Complete Response – 9-2-09** **Complete Response – 4-25-12** **AP – 1-25-13**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	**1-25-13 (final agreed)**
• Original applicant-proposed labeling	**7-25-11**
• Example of class labeling, if applicable	**Package inserts for Januvia (sitagliptin) and Actos (pioglitazone)**

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	**1-25-13 (final agreed)**
• Original applicant-proposed labeling	**7-25-11**
• Example of class labeling, if applicable	**Medication Guide for Januvia (sitagliptin) and Actos (pioglitazone)**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	**1-18-13**
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	**1-27-09, 1-28-09, 12-23-11** **1-7-09, 10-21-11, 12-23-11, 3-27-12, 10-24-12, 10-26-12**
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM **10-9-08, 3-6-12** ☒ DMEPA **3-23-12, 10-19-12, 1-14-13, 1-18-13** ☒ DRISK **2-18-09** ☒ DDMAC **1-18-13** ☐ SEALD ☐ CSS ☒ Other reviews **DMPP 4-20-12, 1-18-13**
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	**11-24-08 (RPM filing review)** ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included **1-29-13**
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC: **1-11-12** If PeRC review not necessary, explain: • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	**9-29-08, 10-9-08, 10-28-08, 11-5-08, 12-2-08, 4-3-09, 5-1-09, 5-20-09, 6-9-09, 12-15-09, 4-20-10, 5-5-10, 9-23-10, 4-20-11, 5-26-11, 7-14-11, 7-21-11, 7-28-11, 8-10-11, 8-15-11, 8-31-11, 9-7-11, 9-21-11, 9-27-11, 10-24-11, 10-27-11, 11-16-11, 11-16-11, 12-5-11, 12-8-11, 12-14-11, 1-13-12, 1-26-12, 2-15-12, 2-17-12, 3-1-12, 3-1-12, 3-15-12, 3-20-12, 3-26-12, 3-27-12, 3-30-12, 4-2-12, 4-16-12, 4-18-12 (2), 5-9-12, 6-26-12, 7-30-12, 8-10-12, 9-13-12, 9-21-12, 9-26-12, 11-5-12, 12-20-12, 1-2-13, 1-4-13, 1-7-13, 1-8-13, 1-14-13, 1-18-13, 1-23-13, 1-25-13, 1-25-13, 1-25-13**
❖ Internal memoranda, telecons, etc.	☒ None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	**2-23-10, 6-29-12**
• Pre-NDA/BLA meeting *(indicate date of mtg)*	**5-7-08 and 6-2-08 (Written Response)**
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	**Pre-IND: 2-8-06** **Type C: 6-20-11**
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	**9-2-09, 4-25-12, 1-25-13**
Division Director Summary Review *(indicate date for each review)*	**9-2-09, 4-25-12, 1-24-13**
Cross-Discipline Team Leader Review *(indicate date for each review)*	**4-20-12**
PMR/PMC Development Templates *(indicate total number)*	☐ None **1-24-13**
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ None **See CDTL review**

[5] Filing reviews should be filed with the discipline reviews.

• Clinical review(s) *(indicate date for each review)*	**7-1-09, 2-24-10, 8-9-11, 2-29-12, 1-21-13**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**Pages 21-22 of Clinical review dated 7-1-09** **Page 24 of Clinical review dated 2-29-12** **Page 22 of Clinical review dated 1-21-13**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	**2-22-12, 4-25-12, 5-8-12, 11-10-12 (Liver safety review)**
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	**8-22-11 (Memo), 8-23-11 (Letter)** **2-16-12, 1-3-13 (DRISK review)**
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	**Summaries: 5-29-09, 2-9-12** **Letters: 4-14-09, 5-29-09, 6-18-09** **Consult: 1-14-13**
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	**8-7-09, 8-8-11, 11-18-11**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	**11-5-08, 6-8-09, 1-18-12, 1-24-12**
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	**6-19-09, 7-30-09**

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	**8-26-09, 4-24-12**
• Supervisory Review(s) *(indicate date for each review)*	**6-8-09, 1-18-12**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**10-21-08, 6-8-09, 1-18-12, 8-27-12**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ None
❖ ECAC/CAC report/memo of meeting	☒ None
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	**7-21-09**
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	**10-28-08, 3-30-09, 6-5-09, 6-12-09, 6-18-09, 7-11-11, 8-2-11, 12-22-11, 1-4-12, 12-12-12, 1-22-13**
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**Page 99 of Product Quality review dated 10-28-08**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: **1-22-13** ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: **N/A** ☐ Acceptable ☐ Withhold recommendation

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD E WHITEHEAD
01/29/2013

From:	Whitehead, Richard
To:	"Cosner, Sandra (TGRD)"
Cc:	Barnes-Glait, Diane (TGRD)
Subject:	NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft MedGuides
Date:	Friday, January 25, 2013 9:43:00 AM
Attachments:	Nesina- MedGuide final.doc Oseni-MedGuide final.doc Kazano MedGuide final.doc

---

Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) Medication Guides (MG) and we accept all revisions to the MGs dated January 24, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, January 24, 2013 2:22 PM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: Nesina, Oseni, Kazano MedGuides Review
Importance: High

Hello Rich,
Please see Takeda's comments in the attached medication guides for the alogliptin products. We accepted all the Agency's comments with the exception of one comment in the OSENI (alo/pio) Medication Guide.

Please let us know if you have any questions.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

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sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, January 24, 2013 10:47 AM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: Nesina, Oseni, Kazano MedGuides Review

Sandy,

I am forwarding the next round of comments from Patient Labeling for the Nesina, Oseni, and Kazano MedGuides. We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you. Because of the tight timelines was ask the you complete your review and return comments by **COB today (January 24)** .

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/25/2013

From:	Whitehead, Richard
To:	"Cosner, Sandra (TGRD)"
Cc:	Barnes-Glait, Diane (TGRD)
Subject:	NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs
Date:	Friday, January 25, 2013 11:52:00 AM
Attachments:	Kazano- PI final.doc Nesina-PI final.doc Oseni-PI final.doc

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Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) prescribing information (PI) and we accept all revisions to the PIs dated January 25, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products; (t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Friday, January 25, 2013 11:32 AM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs

Dear Rich,
We have received this email. We are in agreement with these as the final versions with one exception. We noticed there was a formatting issue we had with Table 3 only in the Oseni label. Therefore, we had to extend the row in order for the AE of "upper respiratory tract infection" to be fully visible. I have made that correction and have reattached this label to you. I am also reattaching the other package inserts with no changes as you have sent them to us.
Please let me know if you need anything further.
Kind regards,
Sandy

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, January 25, 2013 8:44 AM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs

Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) prescribing information (PI) and we accept all revisions to the PIs dated January 24, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, January 24, 2013 11:51 AM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: NDA22271/22426/203414 alogliptin: draft labeling
Importance: High

Dear Rich,
Please find Takeda's edits to the alogliptin product package inserts attached. Please let us know if you need anything further.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
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sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Wednesday, January 23, 2013 3:30 PM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271/22426/203414 alogliptin: draft labeling

Sandy,

Please find attached our next round of edits to the package inserts for alogliptin, alogliptin-pioglitazone, and alogliptin-metformin, incorporating comments from Clinical. We ask you to carry all relevant comments from the alogliptin label to the alogliptin-pioglitazone and alogliptin-metformin labels. The MedGuides are not being provided at this time.

We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you. Because of the tight timelines was ask the you complete your review and return comments **by noon Thursday, January 24th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

###
The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and is the property of Takeda. Unauthorized use, disclosure, or copying of this communication, or any part thereof, is strictly prohibited and may be unlawful. If you received this communication in error, please notify me immediately by return e-mail and destroy this communication and all copies thereof, including all attachments.

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/s/

RICHARD E WHITEHEAD
01/25/2013

From:	Whitehead, Richard
To:	"Cosner, Sandra (TGRD)"
Cc:	Barnes-Glait, Diane (TGRD)
Subject:	NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs
Date:	Friday, January 25, 2013 9:43:00 AM
Attachments:	Nesina-PI final.doc Oseni-PI final.doc Kazano- PI final.doc

---

Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) prescribing information (PI) and we accept all revisions to the PIs dated January 24, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products; (t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, January 24, 2013 11:51 AM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: NDA22271/22426/203414 alogliptin: draft labeling
Importance: High

Dear Rich,
Please find Takeda's edits to the alogliptin product package inserts attached. Please let us know if you need anything further.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
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T 224-554-1957
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sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Wednesday, January 23, 2013 3:30 PM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271/22426/203414 alogliptin: draft labeling

Sandy,

Please find attached our next round of edits to the package inserts for alogliptin, alogliptin-pioglitazone, and alogliptin-metformin, incorporating comments from Clinical. We ask you to carry all relevant comments from the alogliptin label to the alogliptin-pioglitazone and alogliptin-metformin labels. The MedGuides are not being provided at this time.

We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you. Because of the tight timelines was ask the you complete your review and return comments **by noon Thursday, January 24th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/25/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com); Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject: RE: Nesina, Oseni and Kazano PMR- request for clarification
Date: Wednesday, January 16, 2013 12:30:00 PM

Sandy,

See responses to your inquiries below in red. Let me know if you have any additional questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD)
Sent: Tuesday, January 15, 2013 10:09 AM
To: 'Whitehead, Richard'
Cc: Barnes-Glait, Diane (TGRD)
Subject: Nesina, Oseni and Kazano PMR- request for clarification

Dear Rich,

Thank you very much for providing the postmarketing requirements (PMR) for the alogliptin family of products yesterday following the teleconference. Takeda has reviewed the requests and has a couple points of clarification for the Agency in order to develop the most accurate timelines:

For Nesina NDA22271
Regarding PMR #1:

The current pediatric protocol for the ongoing PK study SYR-322_104 [Amendment #8 submitted to IND 69707 Mar 22, 2012 (S/N 672)] specifies different age ranges for the two groups being examined. The protocol specifies that Group 1 is 10 to 13 year olds, inclusive and Group 2 is 14 to 17 year olds, inclusive. Further, the protocol specifies that at least 6 subjects (25%) will be in Group 1 and 18 subjects (75%) will be randomized in Group 2. In addition to submitting all versions of the protocol to the Agency, this study design has been agreed with the Paediatric Committee (PDCO) at the European Medicines Agency. Therefore, Takeda would propose that the age requirements in the PMR match the protocol as currently specified (i.e. 25% of subjects 10 to 13 year olds, inclusive and 75% of subjects 14 to 17 year olds, inclusive). Is this acceptable to the Agency? The Agency finds this acceptable.

Regarding PMR #4:

Takeda would like to seek guidance on the content of the protocol for the enhanced

pharmacovigilance (PV) program. Takeda would propose that this protocol would not conform to a typical clinical study protocol, but would contain the following information:

1. Criteria for collection of information
2. Process for collection of information, including data collection forms
3. Requirement for reporting findings on an annual basis, including format of the analysis

Will this type of information satisfy the Agency's requirement for a protocol to address enhanced pharmacovigilance? If not, can the Agency provide Takeda with additional information as to the requirements for a protocol for an enhanced PV program? The Agency is OK with your proposal; however, in addition to the annual report, expedited reporting of these events is required:

> Expedited reporting to FDA of all initial and follow-up reports of hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis with a serious outcome, and severe hypersensitivity reactions.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
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/s/

RICHARD E WHITEHEAD
01/23/2013

From:	Whitehead, Richard
To:	Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc:	Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject:	Nesina, Oseni, Kazano MedGuides Review
Date:	Friday, January 18, 2013 3:12:00 PM
Attachments:	marked --alogliptin-metformin (Kazano) 203414 DMPP MG Jan 2013.doc marked-alogliptin-pioglitazone (Oseni) 22426 DMPP MG Jan 2013 .doc alogliptin (Nesina) 22271 DMPP MG Jan 2013 (marked).doc

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Sandy,

I am forwarding the first round of comments from Patient Labeling for the Nesina, Oseni, and Kazano MedGuides. We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please note that not all reviewers have looked at this yet so more comments may come on Tuesday, however at this point they should not be extensive (but as always that could change).

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you. Because of the tight timelines was ask the you complete your review and return comments by **7AM Tuesday, January 22nd** .

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/18/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc: Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject: Nesina, Oseni, and Kazano: PMR
Date: Monday, January 14, 2013 2:20:00 PM
Attachments: Postmarketing Requirements for Nesina1102013.doc

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Dear Sandy,

As discussed at today's telephone conference I am forwarding a copy of Postmarketing requirements for Nesina, Oseni, and Kazano should your product(s) be approved. We request that you provide dates for study completion, final reports, etc., as described in the in the document. Email all requested information to me within two days of receipt of this notification. You do not have to submit these officially to the applications. Please confirm receipt of this email.

Regards,

Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

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/s/

RICHARD E WHITEHEAD
01/14/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin: Information Request
Date: Tuesday, January 08, 2013 4:48:00 PM

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response Wednesday, January 9th. Let me know if you have any questions and please confirm receipt of this email notification.

"In your 2nd resubmission the following table was provided for EXAMINE which led FDA to request the incidence of transaminase elevations be summarized for pooled Phase 2/3 trials.

Table 7 Number and Percentage of Subjects With Markedly Abnormal ALT Values (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result			
	Baseline		Post-Baseline	
Parameter (Criterion)	Placebo N=1466	Alogliptin N=1467	Placebo N=1372	Alogliptin N=1387
ALT (>20×ULN)	0	0	0	0
ALT (>10×ULN)	1 (0.1%)	2 (0.1%)	0	5 (0.4%)
ALT (>8×ULN)	1 (0.1%)	2 (0.1%)	0	6 (0.4%)
ALT (>5×ULN)	2 (0.1%)	5 (0.3%)	1 (0.1%)	10 (0.7%)
ALT (>3×ULN)	13 (0.9%)	18 (1.2%)	5 (0.4%)	17 (1.2%)
>3×ULN and total bilirubin >2.0 mg/dL	0	0	0	0
>3×ULN and total bilirubin >2×ULN	0	0	0	0

Source: Appendix 8, Table 4.
Note: The Baseline visit window includes all results obtained on or before the date of randomization.

When we compare Table 7 to the updated table provided in Takeda's 1/7/13 response in email below and pasted here, there are 4 patients on alogliptin w/ ALT > 10xULN in the 'during treatment' column but 5 patients in Table 7 w/ ALT > 10xULN in the post-baseline column. Please explain this discrepancy of one patient."

Number (%) of Subjects With ≥1 Marked Abnormal Result						
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389
ALT >3×ULN and total bilirubin >2×ULN	0	0	1 (0.04)	1 (0.04)	0	1 (0.04)
ALT >20×ULN	0	0	1 (0.04)	0	0	0
ALT >10×ULN	1 (0.04)	2 (0.08)	2 (0.08)	4 (0.17)	0	1 (0.04)
ALT >5×ULN	2 (0.08)	2 (0.08)	12 (0.51)	19 (0.80)	2 (0.08)	5 (0.21)
ALT >3×ULN	10 (0.42)	14 (0.59)	32 (1.35)	44 (1.84)	8 (0.34)	12 (0.50)

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Monday, January 07, 2013 1:35 PM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request

Hello Rich,
Please see Takeda's response to FDA's Jan. 4 request in the attached.
I will also submit this as a formal submission to the NDA's, hopefully by the end of today.
Please let me know if you need anything else.
Kind regards,
Sandy

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, January 04, 2013 6:36 AM
To: Cosner, Sandra (TGRD)
Subject: NDA22271 alogliptin: Information Request

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAMINE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/08/2013

From: Whitehead, Richard
To: "Cosner, Sandra (TGRD)"
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request
Date: Monday, January 07, 2013 8:54:00 AM

Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. We ask that you provide your response by noon, today. Let me know if you have any questions and please confirm receipt of this email notification.

Please explain how you were able to determine that subject 8413-006/402 was assigned to placebo and yet state that this "case currently remains blinded as this is an ongoing study in the safety database". Did you not have to unblind the case to determine treatment assignment?

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Sunday, January 06, 2013 10:11 PM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Jan. 4 Information Request

Dear Rich,

During our evaluation of FDA's latest information request from Friday, Jan. 4 for an update of Table 3f (Markedly abnormal values for hepatic parameters of Study 402), Takeda re-ran the Table with a new database cut (with 6 months of additional data) and has unfortunately learned of an incorrect treatment code on the case of interest in Study 402; subject 8413-006/402 (TPG2012A01058) that was provided to FDA in the July 2012 NDA resubmission. Takeda had inadvertently assigned this case to the alogliptin 25 mg treatment code and subsequently upon this latest review learned that this subject was in fact on placebo.

We would like to reassure the Agency that the statistical tables and outputs from the clinical database are accurate. In addition, the safety database is accurate and this case currently remains blinded as this is an ongoing study in the safety database. This error was in part due to the fact

that this subject was a late breaker case that occurred following the database cut off and that the table in 2.7.4 was manually generated. Because this error was discovered, the team is putting extra effort in QCing all the data in all manually generated hepatic tables from the NDA resubmission (i.e., Tables 3c, 3d and 3i) to confirm these are accurate. The team is also re-checking all current data, randomization codes, and conducting QC checks against previous and current database cut offs. Takeda apologizes and regrets very much that this error has occurred. We understand this case was of specific interest to both Takeda and FDA and we wanted to notify you as soon as we had confirmed this error. Through our investigation, we are ensuring that no other such mis-assignments exist. The case will be properly reflected in our submission that we will be sending to you by the end of the day tomorrow (Jan 7) as per the data you requested last week, at which time the quality control of the other tables will have been completed as well.

We understand the Agency is meeting Monday, January 7 for the second round of labeling comments and potentially later in the week for the end-of-review wrap-up meeting. If the Division has any concerns or would like any additional clarification on this issue, Takeda would gladly be available for a teleconference to further review the details of this finding and provide clarity or additional assurances ensuring data integrity.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

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sandra.cosner@takeda.com
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From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, January 04, 2013 6:36 AM
To: Cosner, Sandra (TGRD)
Subject: NDA22271 alogliptin: Information Request

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAMINE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/07/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin: Information Request
Date: Friday, January 04, 2013 7:36:00 AM

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAMINE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/04/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin: Information Request
Date: Wednesday, January 02, 2013 12:40:00 PM
Attachments: image005.png
image006.png

Dear Sandy,

Please provide a response to the following questions for alogliptin NDA22271. Send your response to this Information request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Friday, January 4, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. What doses of alogliptin were prescribed to the patients who experienced the two postmarketing events (TCI2011A04573 (fulminant hepatic failure) and TCI2011A06837 (transaminitis and jaundice)?

2. Please provide summary of incidence of transaminase elevations as in the following table but broken down by actual daily alogliptin doses used in all these trials (6.25, 12.5, 25 and 50 mg).

Table 3.b Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Controlled Phase 2 and 3 Study Group)

	Number (%) of Subjects With Markedly Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
Parameter	All Comparators (d) N=5786	All Alogliptin (e) N=9608	All Comparators N=5786	All Alogliptin N=9608	All Comparators N=5699	All Alogliptin N=9495
ALT (>3×ULN) and total bilirubin >2×ULN	0	0	3 (0.05) [0.07]	2 (0.02) [0.03]	2 (0.04)	1 (0.01)
ALT (>20×ULN)	0	0	3 (0.05) [0.07]	3 (0.03) [0.04]	2 (0.04)	2 (0.02)
ALT (>10×ULN)	1 (0.02)	3 (0.03)	5 (0.09) [0.11]	12 (0.12) [0.17]	3 (0.05)	4 (0.04)
ALT (>5×ULN)	2 (0.03)	6 (0.06)	17 (0.29) [0.39]	34 (0.35) [0.49]	7 (0.12)	11 (0.12)
ALT (>3×ULN)	16 (0.28)	41 (0.43)	89 (1.54) [2.04]	126 (1.31) [1.82]	30 (0.53)	32 (0.34)
ALP (>3×ULN)	3 (0.05)	3 (0.03)	9 (0.16) [0.21]	18 (0.19) [0.26]	5 (0.09)	8 (0.08)
Bilirubin, total (>2.0 mg/dL)	11 (0.19)	19 (0.20)	42 (0.73) [0.96]	55 (0.57) [0.79]	22 (0.39)	24 (0.25)

Source: IAS Table 5.1.1, 5.1.2, 5.6.1, and 5.6.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) The number of subjects with marked abnormalities per 100 subject-years of exposure is presented in brackets.
(c) Last assessment is the last assessment of ALT on or before the last dose of study medication.
(d) The All Comparators grouping combines placebo and active comparator dose groups.
(e) The All Alogliptin grouping combines the 6.25, 12.5, 25, 50, and 100 mg dose groups.

3. In the following table of transaminase elevations in EXAMINE provided by Takeda, did this table include case 8413-006/402? "

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/02/2013

From:	Whitehead, Richard
To:	Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc:	Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject:	NDA22271/22426/203414 alogliptin: draft labeling
Date:	Thursday, December 20, 2012 10:55:00 AM
Attachments:	alo-met- 20Dec12-package-insert.doc alo-pio-20Dec12-draft-package-insert.doc alogliptin 20Dec12-PI.doc

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Sandy,

Please find attached our first round of edits to the package inserts for alogliptin, alogliptin-pioglitazone, and alogliptin-metformin, incorporating comments from Clinical, CMC, Pharm/Tox, Statistics and Clinical Pharmacology. As previously mentioned we were able to spend more time reviewing the alogliptin label, therefore we ask you to carry all relevant comments from the alogliptin label to the alogliptin-pioglitazone and alogliptin-metformin labels.

We have one note from the nonclinical review team:

"We have provided editorial changes to the pregnancy (8.1) and carcinogenesis (13.1) sections of the alogliptin monotherapy (NESINA) and alogliptin + pioglitazone (OSENI) labels. We feel the nonclinical data in question does not need to be described because the animal findings at the high exposure margins would not provide additional meaningful information about clinical risks. "

We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you. Because of the tight timelines was ask the you complete your review and return comments by **noon, Thursday, January 3rd**.

We also request that you convert the alogliptin and alogliptin-metformin Patient Package Inserts into MedGuides and update the alogliptin-pioglitazone MedGuide. Because of the serious risk of hepatotoxicity associated with the use of alogliptin and the serious risk of pancreatitis related to the DPP4 class, FDA has determined that alogliptin and alogliptin/metformin will be required to have a Medication Guide. Additionally, because of the serious risks of hepatotoxicity and heart failure associated with the use of alogliptin/pioglitazone and the serious risk of pancreatitis related

to the DPP4 class, FDA has determined that alogliptin/pioglitazone will be required to have a Medication Guide (which it does, but needs to include the additional risks).

Please confirm receipt of this email, and let me know if you have any questions. Once you've had a chance to review our comments, please let me know when we can expect to receive your response.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
12/20/2012

From: Cosner, Sandra (TGRD)
To: Whitehead, Richard
Subject: RE: NDA22271/NDA22426/NDA203414 Request for Information
Date: Tuesday, October 30, 2012 3:11:24 PM

Thank you Rich. I am confirming receipt of this email. The team will work on this response and get back with you as soon as we are able to.
Thanks
Sandy

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Monday, October 29, 2012 2:41 PM
To: Cosner, Sandra (TGRD)
Cc: Villinski, Allison (TGRD)
Subject: NDA22271/NDA22426/NDA203414 Request for Information

NDA22271 alogliptin
NDA22426 alogliptin/pioglitazone
NDA203414 alogliptin/metformin

Dear Ms. Cosner:

In reference to NDA 22271, NDA22426, and NDA203414, please see the request for information below. We ask that you provide responses at your earliest opportunity. Let me know if you have any questions and please confirm receipt of this email.

"In your October 5, 2012 Information Request Response, you stated that subject 8413-006/402 was on atorvastatin which was discontinued on day 207. Provide further details regarding the atorvastatin administration, including the date the patient was initially administered atorvastatin, whether atorvastatin was administered consistently from the start date to day 207 (or whether there were any gaps), and any other information you have regarding this case that you have not yet submitted to us.

Submit each individual LSEC committee members' assessment of subject 8413-006/402 .

On October 10, 2012, you submitted follow up safety report TCI2012A05429. Submit any additional information you have regarding this case."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
11/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22426

GENERAL ADVICE

Takeda Pharmaceuticals, U.S.A., Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oseni (alogliptin and pioglitazone) Tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg.

We also refer to your April 13, 2012 submission, containing revised container labels and carton labeling.

We have reviewed the referenced material and have the following comments and recommendations:

1) Sample Packaging (i.e. 7-count bottles, 7-count blister packs [redacted] (b) (4))

2) Blister Card Container Labels (All Strengths)
   a. Include a statement which communicates that the blister pack is not child resistant and to keep out of reach of children.

   b. Revise the day designation on the inner card [redacted] (b) (4) to read the specific day of the week (i.e. Monday, Tuesday, etc.). This is revised from earlier recommendations because it is now believed that specifying the day is more helpful in reminding patients if they took their daily dose. This change should be consistent across all alogliptin-containing products.

3) All commercial and professional container labels and carton labeling for the 12.5 mg/15 mg and 25 mg/30 mg
   Revise the color scheme for either 12.5 mg/15 mg or 25 mg/30 mg, or bot (b) (4) [redacted]

(b) (4)

4) Insert Labeling
   Replace the slash "/" used between the active ingredients in the established name (alogliptin/pioglitazone) with the word "and." The established name should read "(alogliptin and pioglitazone) tablets".

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
10/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022426

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

Attention: Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated September 19, 2008, received September 22, 2008 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Pioglitazone Tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg. Please also refer to your Class 2 Resubmission dated and received July 27, 2012.

We also refer to:

- Your initial proprietary name submission, dated October 18, 2011, for the proposed name Oseni;
- Our initial correspondence dated December 23, 2011, finding this proposed proprietary name conditionally acceptable;
- Your submission dated and received August 1, 2012, requesting re-review of your proposed proprietary name, Oseni.

We have completed our review of the proposed proprietary name, Oseni, and have concluded that it is acceptable.

The proposed proprietary name, Oseni, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 1, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Richard Whitehead at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
10/26/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin Information Request
Date: Wednesday, September 26, 2012 11:31:00 AM

NDA22271 alogliptin Information Request

Dear Sandy:

FDA is requesting the following information in reference to the NDA22271 Fourth Japanese Periodic Safety Update Report for alogliptin:

"In Table 19 of the Fourth Japanese Periodic Safety Update Report for alogliptin, you list 15 nonserious hepatic adverse events. Please answer the following for these cases:

- Did any of the nonserious cases have biochemical Hy's law?
- Did the event resolve? If yes, was use of alogliptin continued?
- If alogliptin was discontinued, was the patient rechallenged?"

Submit your response as amendments to the 3 alogliptin NDAs. Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/DMEP; 10903 New Hampshire Avenue, WO22 Room 3121, Silver Spring, MD 20993; 301.796.4945; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
09/26/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271/NDA22426 Information Request
Date: Friday, September 21, 2012 7:49:00 AM

NDA 22271 alogliptin

NDA 22426 alogliptin/pioglitazone FDC

Sandy,

FDA is requesting that you provide the information below to NDA 22271 and NDA 22426.

"On August 16, 2012, you submitted an updated pediatric deferral request containing revised clinical study dates to alogliptin/metformin FDC NDA 203-414 but not alogliptin NDA 222-71 or alogliptin/pioglitazone FDC NDA 22-426. Please submit the updated pediatric deferral information to NDAs 22-271 and 22-426."

Let me know if you have any questions. Please confirm receipt of this email.

Regards,

Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
09/21/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA 022426 and NDA 022271 Acknowledge- Class 2 Response Letters
Date: Wednesday, September 12, 2012 2:50:00 PM

NDA 022426
NDA 022271

Dear Ms. Cosner:

In reference to the Acknowledge- Class 2 Response Letters sent for NDA 022426 and NDA 022271 on August 10, 2012, please note that the user fee goal date is not correct in each letter. The correct user fee goal date for NDA 022426 should state **January 27, 2013** and for NDA 022271 the date should be **January 26, 2013**. Let me know if you have any questions. Please confirm receipt of this email

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
09/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022426

ACKNOWLEDGE – CLASS 2 RESPONSE

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

We acknowledge receipt on July 27, 2012, of your July 27, 2012, resubmission of your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin-pioglitazone fixed-dose combination tablets.

We consider this a complete, class 2 response to our action letter dated April 25, 2012. Therefore, the user fee goal date is **January 27, 2012**.

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEHREEN HAI
08/10/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Monday, July 30, 2012 1:36 PM
To: 'sandra.cosner@takeda.com'
Cc: Hai, Mehreen
Subject: Information needed for NDAs 22-271 and 22-426

Dear Sandra,

We are reviewing the CMC section of your NDAs mentioned above and need the following clarification and information from you as soon as possible:

1. Include all the facilities information (facility address, contact name, phone number and fax number) in the Form 356H and clearly state whether there is any change in the commercial manufacturing or testing facility since the last submission for both the NDAs (i.e. new sites or deleted sites).
2. Please state if the resubmission includes any new CMC information.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested. Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you

Khushboo Sharma
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
07/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 29, 2012. The purpose of the meeting was to discuss the deficiencies described in our Complete Response letter dated April 25, 2012, and to discuss actions to be taken to address these deficiencies.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes for End-of-Review meeting held on June 29, 2012

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Review
Meeting Date and Time:	June 29, 2012, 2:00 p.m. – 3:00 p.m.
Meeting Location:	White Oak Campus, Silver Spring, MD
Application Numbers:	NDA 022271; NDA 022426
Product Names:	Alogliptin tablets; Alogliptin-pioglitazone fixed-dose combination tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Mehreen Hai, Ph.D.

FDA ATTENDEES

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
Jean-Marc Guettier, M.D.	Diabetes Clinical Team Leader, DMEP
Karim Calis, Pharm.D.	Acting Diabetes Clinical Team Leader, DMEP
Lisa Yanoff, M.D.	Clinical Reviewer, DMEP
Janice Derr, Ph.D.	Biostatistics Reviewer, Division of Biometrics II
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII
Eugenio Andraca-Carrera, Ph.D.	Biostatistics Reviewer, Division of Biometrics VII
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology 2
Manoj Khurana, Ph.D.	Reviewer, Division of Clinical Pharmacology 2
Leonard Seeff, M.D.	Hepatologist, Office of Surveillance and Epidemiology (OSE)
Christian Hampp, Ph.D.	Pharmacoepidemiologist, Division of Epidemiology 1 (OSE)
Caitlin Knox	Fellow, Division of Epidemiology 1 (OSE)

SPONSOR ATTENDEES (Takeda Representatives and Consultants)

Sandra Cosner, R.Ph.	Associate Director, Regulatory Affairs
Penny Fleck, M.T.	Senior Director, Clinical Science
Thomas Harris, R.Ph.	Global Regulatory Head, Regulatory Affairs
Qais Mekki, MD, Ph.D.	Vice President, Pharmacovigilance
Melvin Munsaka, Ph.D.	Senior Manager, Safety Statistics
Azmi Nabulsi, M.D.	President, Takeda Global Research and Development
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Neila Smith, M.D.	Executive Medical Director, Pharmacovigilance
Nancy Siepman, Ph.D.	Vice President, Analytical Sciences
Thomas Strack, M.D.	Therapeutic Area Head, Diabetes, Pharmaceutical Drug Development
Allison Villinski, M.S.	Director, Regulatory Affairs
(b) (4)	(b) (4) (Consultant)
(b) (4)	(b) (4) (Consultant)

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 021073 (proprietary name: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009, for NDA 022426.

TGRD resubmitted both NDAs on July 25, 2011. A complete response letter issued for both NDAs on April 25, 2012.

The purpose of this meeting is to discuss the resubmissions that will respond to the April 25, 2012, complete response letter.

2. DISCUSSION

The sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the sponsor on June 26, 2012, follow in **bold** font. A summary of the meeting discussion is indicated in *italicized* font.

Preliminary Discussion: Takeda summarized the timeline of the alogliptin NDA. A total of 9,857 subjects have been exposed to alogliptin in the April 2012 IAS safety update (6,934 subject-years). (b) (4) *stated that, if alogliptin is associated with hepatotoxicity, it is a rare event (1:1000,000).* (b) (4) *acknowledged there was an imbalance in serum ALT>10x ULN in the clinical trial database and stated that the risk of hepatotoxicity cannot be excluded. However, he believes the risk is finite and not severe.*

Question 1: Provided that the Agency's review of the new clinical and postmarketing data are consistent with Takeda's interpretation of the data summarized in this briefing document, does the Agency agree that the information planned for submission can provide the additional reassurance the FDA is seeking on the hepatic safety profile of alogliptin in order to complete the review and approve the applications?

FDA Preliminary Response: Whether or not the information planned for submission can provide the additional reassurance necessary for approval is a review issue. However, the April 2012 IAS exposure sufficiently exceeds that of the July 2011 submission, so as to justify submission of the data for a complete review.

Meeting Discussion: *The Agency and Takeda agreed that information similar to that contained in the meeting document could be submitted to the NDAs as a complete response. Although final determination of whether such submission is a Type 1 or 2 complete response would be made after submission, it would likely be a Type 2 response with a six-month review clock because it contains clinical data.*

Question 2: Takeda's understanding per the CRL [complete response letter] is that the resubmission must be supported by the absence of any postmarketing reports of severe drug-induced liver injury events that are convincingly linked to alogliptin therapy (e.g., leading to death or liver transplantation). Takeda would like to clarify that any such case would need to be devoid of confounding factors prior to the Agency attributing the event to alogliptin (or any drug) therapy. This should especially be the case in light of the current lack of liver case imbalance in the clinical database. Does the Agency agree?

FDA Preliminary Response: A case need not be devoid of all confounding factors prior to attributing the event to alogliptin therapy. Although the assessment of potential drug-induced liver injury is grounded in the scientific grading system developed by the National Institutes of Health Drug-Induced Liver Injury Network (DILIN) Study Group, the Agency recognizes that, at times, the final classification of a particular case may be a matter of opinion. Consistent with the DILIN Study Group grading system, an attempt will be made to assess the effect of potential confounders before attributing causality to drug therapy.

Meeting Discussion: *There was no discussion of Question 2.*

Question 3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

FDA Preliminary Response: We generally agree with the proposed structure and contents of the NDA resubmission. However, the Summary of Clinical Safety in Module 2 should also contain the following:

- **Summary of deaths**
- **Updated summary tables for cardiovascular safety, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy, fractures, and hypoglycemia. Please include a summary of the changes from the previous submission.**

Pre-Meeting Response from Takeda: *In response to Question #3, Takeda would like to clarify how each of the requested topics will be addressed within 2.7.4. As had been done previously, narratives for all deaths, serious adverse events and adverse events leading to discontinuation will be included. For the Controlled Phase 2/3 dataset proposed for the NDA re-submissions, any key differences from the July 2011 NDA re-submissions will be highlighted in text.*

Does the Agency agree with the following proposals for each of the topics below?

• Summary of deaths: A summary by System Organ Class (SOC) and Preferred Term (PT) for Controlled Phase 2/3 Group will be provided.

• CV Safety: An updated MACE Analysis using adjudicated CV events would include data from Study 402 (July 2011 based on pre-specified interim analysis), 305 (1 year pre-planned interim data cut), 302 (completed clinical study) and those studies previously included in the July 2011 NDA re-submissions. Please note that the CV SOC will be presented and discussed in AE and SAE sections of 2.7.4.

• Renal Safety: The renal data based on clinical laboratory values will be updated for the Controlled Phase 2/3 data set.

• Hypersensitivity: The hypersensitivity section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.

• Skin Lesions: The hypersensitivity cluster includes angioedema, anaphylactic reaction and severe cutaneous skin reactions (which covers rash and puritis). Does the Agency agree this cluster is sufficient with regards to skin lesions?

• Pancreatitis: The pancreatitis section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.

• Infections: Adverse events will be presented by SOC of Infections and Infestations similar to that in July 2011 NDA re-submissions.

• Malignancy: Takeda will utilize the SMQ of malignancies similar to that included in the July 2011 NDA re-submissions.

• Fractures: Can the Agency clarify if this request is due to pioglitazone component of the fixed dose product? If so, there are no new studies with the alogliptin/pioglitazone combination since

the July 2011 resubmission; therefore no new information would be included in the upcoming NDA re-submissions.

• *Hypoglycemia: The studies with similar definitions of hypoglycemia will be integrated; however some studies over the course of the program have a different definition of hypoglycemia and Takeda proposes to discussed those results individually.*

Meeting Discussion: *The Agency agreed with Takeda's Pre-Meeting Response, although it was agreed that Takeda would also submit an analysis of Potential Cutaneous Drug Reactions (PCDR's) as it had done in the previous NDA submission. The Agency clarified that the fracture request was due to the pioglitazone component of the fixed-dose product, therefore the Agency understands that no new updates will be provided for fractures as there are no additional clinical data with alogliptin-pioglitazone.*

The Agency stated that it recently received guidance from FDA Counsel and staff in the Division of Information and Disclosure Policy on whether interim data from the ongoing cardiovascular (CV) trial can be withheld from public disclosure. It is not CDER's practice to redact summary data from approval documents when the Center relies on such information to make an approval decision. CDER is committed to transparency of our decision-making processes. We believe that it is important for the public to understand that CDER carefully evaluated the benefits and risks of a particular therapy for a certain condition of use and to understand how we came to our decision that the benefits outweigh the risks. Furthermore, FDA's regulations favor disclosure of information in an application after the application has been approved and identify the summary safety data that are subject to disclosure immediately upon issuance of an approval letter. The Agency is not inclined to place the data in the label.

Takeda inquired whether other regulatory agencies share a similar view regarding disclosure policy as FDA. The Agency is aware that other regulatory agencies are also inclined toward complete disclosure and that, in some cases, these regulatory agencies would also consider labeling of interim data.

Question 4: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, we agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable.

Meeting Discussion: *There was no discussion of Question 4.*

Question 5: Does the Agency agree with Takeda's plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Yes, we agree with the plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not to submit a separate summary report of the integrated analyses within Module 5.3.5.3.

Meeting Discussion: *There was no discussion of Question 5.*

Question 6: Since Studies 402 and 305 are still ongoing, Case Report Forms for these studies will not be included in the NDA resubmissions as agreed upon for the July 2011 resubmission with regard to Study 402. Is this proposal acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable. However, additional information may be requested if it is needed.

Meeting Discussion: *There was no discussion of Question 6.*

Question 7: Takeda does not plan to summarize data from the recently completed, 4-year, open-label extension study (012) within 2.7.4. However, the final clinical study report will be provided in the resubmission. Is this approach acceptable to the Agency?

FDA Preliminary Response: Yes, we agree with your plan to not summarize data from uncontrolled, open-label extension study (012) within 2.7.4.

Meeting Discussion: *There was no discussion of Question 7.*

Question 8: Takeda plans to update the efficacy section of the alogliptin package insert based on data from Studies MET-302 (b) (4) Since the efficacy information is not integrated, Takeda does not plan to include a Clinical Summary of Efficacy (2.7.3) in the NDA resubmission but will rely on the data included in the individual clinical study reports. Is the Agency agreeable to this approach?

FDA Preliminary Response: (b) (4) **we agree with your plan to update the efficacy section of the alogliptin package insert with data from completed study MET-302. Since the efficacy information is not integrated, we agree with your plan to not include a Clinical Summary of Efficacy (2.7.3) in the resubmission.**

Meeting Discussion: (b) (4)

The Agency and Takeda agreed that safety (b) (4) *data from ongoing study 305 could be included in the label.*

Question 9: Due to the fact that labeling negotiations had initiated under the previous review cycle and there are still some aspects other than safety that need to be discussed, Takeda proposes not to include Structured Product Labeling (SPL) in the NDA resubmissions. Takeda will provide the package insert information in SPL format once labeling language has been agreed upon by both Takeda and the Agency. Is this acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable.

Meeting Discussion: *There was no discussion of Question 9.*

Question 10: Does the Agency agree with the process for enhanced monitoring of postmarketing liver-related cases?

FDA Preliminary Response: Yes, we agree with the process for enhanced monitoring of postmarketing liver-related cases.

Meeting Discussion: *There was no discussion of Question 10.*

Question 11: During the course of the review of the NDA resubmissions, spontaneous reports related to hepatic safety may be received. Takeda will continue to expedite these reports to the INDs and NDAs, as previously agreed. However, in an effort to provide a meaningful adjudication of these cases, Takeda often needs adequate time to gather relevant information for an individual postmarketing case. Therefore, the LSEC will review new cases on a monthly basis, and their assessments will be subsequently submitted to the Agency. Is this approach reasonable to the Agency?

FDA Preliminary Response: Yes, your approach is reasonable. However, additional information may be requested as needed.

Meeting Discussion: *There was no discussion of Question 11.*

Question 12: If during the course of the review of the NDA resubmissions, there is striking disagreement between the Agency and the LSEC on a particular liver safety case(s), would the Agency consider discussing the case(s) with the LSEC (and Takeda)?

FDA Preliminary Response: Yes, we may consider discussing case(s) with you and the LSEC. However, the purpose of such discussion would be to share information to ensure that both you and the Agency have all currently available data to aid decision-making. The objective of the meeting would not be to obtain a consensus of opinion on liver case(s) or to discuss upcoming regulatory decision(s).

Meeting Discussion: *There was no discussion of Question 12.*

Question 13: Is the Agency agreeable to discussing how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End of Review meeting?

FDA Preliminary Response: Yes, we may discuss how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End-of-Review meeting.

Meeting Discussion: *It was agreed that Takeda could submit data from the April 2012 IAS Update to the alogliptin/metformin FDC NDA as a major amendment. The goal dates for the alogliptin/metformin FDC NDA and the alogliptin and alogliptin/pioglitazone FDC NDAs will not be perfectly aligned and discretion may be taken with regard to the completion dates for any one of these NDAs. However, it was stated that approval of the FDC NDAs is contingent on the Agency's conclusion that the deficiencies for the alogliptin NDA have been adequately addressed and any timing of approval would be based on such a conclusion.*

Question 14: In the 25 April 2012 Complete Response Letter, there are questions related to the alogliptin pediatric program. Takeda is currently planning on initiating the phase 3 program in early 2013 due to Pediatric Committee requirements. In order to incorporate the Agency's feedback into the studies before they are started, Takeda plans to submit responses to the pediatric questions in an IND Amendment. Is this proposal acceptable?

FDA Preliminary Response: You may submit responses to the pediatric questions in an IND amendment. However, please note that a pediatric postmarketing study requirement cannot be issued until an NDA is approved. Please also submit relevant information to the NDA.

Meeting Discussion: *Takeda stated that it wishes to conduct a global pediatric program. As a result, it may need to initiate pediatric study(ies). It asked for the Agency's cooperation in developing the global pediatric development program. The Agency agreed.*

Additional Preliminary Comment from FDA: Please explain whether or not you plan to (b) (4) **could possibly offset the potential liver liability.**

Meeting Discussion: *There was lengthy discussion regarding the CV protocol.* (b) (4). *is planned, if the 1.3 goal is met. However, it was not clear if this was a modification to the previous CV protocol and statistical analysis plan.* (b) (4) *Takeda will consider protocol revisions to the pre-planned interim analyses and will submit any proposed changes for review by the Agency. The Agency*

agreed to review the protocol and expressed that any revision to the interim analyses include clearly defined timing of the interim look, stopping rules, and alpha-spending function.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

Slides presented by the sponsor at the meeting are attached.

NDAs 22-271 and 22-426

FDA End-of-Review Meeting for alogliptin and alogliptin/pioglitazone

June 29, 2012

Takeda Global Research & Development Center, Inc.

Alogliptin End of Review Meeting - June 29, 2012

- Question 1– adequacy of clinical and postmarketing data to address complete response
- Question 3 – proposed content of the resubmission
- Question 8 – inclusion of efficacy data for studies 302 [redacted] (b) (4) in the package insert
- Question 13 – path forward for the alogliptin/metformin NDA review cycle
- Question 14 – pediatric program
- Additional Comment: regarding [redacted] (b) (4) for EXAMINE trial

Overall Alogliptin Exposure in Controlled Phase 2/3 Studies

	Alogliptin Total Subject Numbers (n)	Alogliptin Cumulative Exposure (Subject-Years)
July 2011 (NDA Re-submission)	5232	2498
November 2011 (Response to 24 October 2011 Information Request)	7229	3378
April 2012 IAS (Proposed NDA Re-submission)	9857	6934

The proposed 2012 re-submission represents a 40% increase in incidence and 100% increase in exposure since November 2011.

Number of Subjects Meeting Markedly Abnormal ALT Criteria in Phase 2/3 Controlled Studies

	November 2011		April 2012 IAS	
	Number (%) of Subjects w/ >=1 Markedly Abnormal Result (95% Exact CI)			
Parameter	**All Comparators (N=4074)**	**All Alogliptin (N=7011)**	**All Comparators (N=5786)**	**All Alogliptin (N=9608)**
ALT>20xULN	0 (0, 0.09)	2 (<0.1) (0, 0.10)	3 (0.1) (0.01, 0.15)	3 (<0.1) (0.01, 0.09)
ALT>10xULN	0 (0, 0.09)	8 (0.1) (0.05, 0.22)	5 (0.1) (0.03, 0.20)	12 (0.1) (0.06, 0.22)
ALT>5xULN	6 (0.1) (0.05, 0.32)	21 (0.3) (0.19, 0.46)	17 (0.3) (0.17, 0.47)	34 (0.4) (0.25, 0.49)
ALT>3xULN	39 (1.0) (0.68, 1.31)	71 (1.0) (0.79, 1.28)	89 (1.5) (1.24, 1.89)	126 (1.3) (1.09, 1.56)

Note: CIs calculated using Binomial Distribution.

Question #3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

- Narratives for all deaths, serious adverse events and adverse events leading to discontinuation will be included.

- For the Controlled Phase 2/3 dataset proposed for the NDA re-submissions, any key differences from the July 2011 NDA re-submissions will be highlighted in text.

- **Summary of deaths:** A summary by System Organ Class (SOC) and Preferred Term (PT) for Controlled Phase 2/3 Group will be provided.

- **CV Safety:** An updated MACE Analysis using adjudicated CV events would include data from Study 402 (July 2011 based on pre-specified interim analysis), 305 (1 year pre-planned interim data cut), 302 (completed clinical study) and those studies previously included in the July 2011 NDA re-submissions. The CV SOC will be presented and discussed in AE and SAE sections of 2.7.4.

- **Renal Safety:** The renal data based on clinical laboratory values will be updated for the Controlled Phase 2/3 data set.

Question #3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

- **Hypersensitivity:** The hypersensitivity section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.
- **Skin Lesions:** The hypersensitivity cluster includes angioedema, anaphylactic reaction and severe cutaneous skin reactions (which covers rash and pruritus). Does the Agency agree this cluster is sufficient with regards to skin lesions?
- **Pancreatitis:** The pancreatitis section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.
- **Infections:** Adverse events will be presented by SOC of Infections and Infestations similar to that in July 2011 NDA re-submissions.
- **Malignancy:** Takeda will utilize the SMQ of malignancies similar to that included in the July 2011 NDA re-submissions.
- **Fractures:** Can the Agency clarify if this request is due to pioglitazone component of the fixed dose product? If so, there are no new studies with the alogliptin/pioglitazone combination since the July 2011 resubmission; therefore no new information would be included in the upcoming NDA re-submissions.
- **Hypoglycemia:** The studies with similar definitions of hypoglycemia will be integrated; however some studies over the course of the program have a different definition of hypoglycemia and Takeda proposes to discussed those results individually.

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/s/

MEHREEN HAI
07/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING PRELIMINARY COMMENTS

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to your correspondence dated and received April 27, 2012, requesting an End-of-Review meeting to discuss the deficiencies described in our Complete Response letter dated April 25, 2012, and to discuss actions to be taken to address these deficiencies.

Our preliminary responses to your meeting questions are enclosed.

Please provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	End-of-Review
Meeting Date and Time:	June 29, 2012, 2:00 p.m. – 3:00 p.m.
Meeting Location:	White Oak Campus, Silver Spring, MD
Application Numbers:	NDA 022271; NDA 022426
Product Names:	Alogliptin tablets; Alogliptin-pioglitazone fixed-dose combination tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 29, 2012 at 2:00 p.m. between Takeda Global Research & Development Center, Inc. and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1. BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 021073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009 for NDA 022426.

TGRD resubmitted both NDAs on July 25, 2011. A complete response letter issued for both NDAs on April 25, 2011.

The purpose of this meeting is to discuss the resubmissions in response to the complete response letter that issued for NDA 022271 and NDA 022426.

2. QUESTIONS AND PRELIMINARY RESPONSES

Your questions are repeated below, followed by our preliminary responses in **bold** print:

Question 1: Provided that the Agency's review of the new clinical and postmarketing data are consistent with Takeda's interpretation of the data summarized in this briefing document, does the Agency agree that the information planned for submission can provide the additional reassurance the FDA is seeking on the hepatic safety profile of alogliptin in order to complete the review and approve the applications?

FDA Preliminary Response: Whether or not the information planned for submission can provide the additional reassurance necessary for approval is a review issue. However, the April 2012 IAS exposure sufficiently exceeds that of the July 2011 submission, so as to justify submission of the data for a complete review.

Question 2: Takeda's understanding per the CRL [complete response letter] is that the resubmission must be supported by the absence of any postmarketing reports of severe drug-induced liver injury events that are convincingly linked to alogliptin therapy (e.g., leading to death or liver transplantation). Takeda would like to clarify that any such case would need to be devoid of confounding factors prior to the Agency attributing the event to alogliptin (or any drug) therapy. This should especially be the case in light of the current lack of liver case imbalance in the clinical database. Does the Agency agree?

FDA Preliminary Response: A case need not be devoid of all confounding factors prior to attributing the event to alogliptin therapy. Although the assessment of potential drug-induced liver injury is grounded in the scientific grading system developed by the National Institutes of Health Drug-Induced Liver Injury Network (DILIN) Study Group, the Agency recognizes that, at times, the final classification of a particular case may be a matter of opinion. Consistent with the DILIN Study Group grading system, an attempt

will be made to assess the effect of potential confounders before attributing causality to drug therapy.

Question 3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

FDA Preliminary Response: We generally agree with the proposed structure and contents of the NDA resubmission. However, the Summary of Clinical Safety in Module 2 should also contain the following:

- **Summary of deaths**
- **Updated summary tables for cardiovascular safety, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy, fractures, and hypoglycemia. Please include a summary of the changes from the previous submission.**

Question 4: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, we agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable.

Question 5: Does the Agency agree with Takeda's plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Yes, we agree with the plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not to submit a separate summary report of the integrated analyses within Module 5.3.5.3.

Question 6: Since Studies 402 and 305 are still ongoing, Case Report Forms for these studies will not be included in the NDA resubmissions as agreed upon for the July 2011 resubmission with regard to Study 402. Is this proposal acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable. However, additional information may be requested if it is needed.

Question 7: Takeda does not plan to summarize data from the recently completed, 4-year, open-label extension study (012) within 2.7.4. However, the final clinical study report will be provided in the resubmission. Is this approach acceptable to the Agency?

FDA Preliminary Response: Yes, we agree with your plan to not summarize data from uncontrolled, open-label extension study (012) within 2.7.4.

Question 8: Takeda plans to update the efficacy section of the alogliptin package insert based on data from Studies MET-302 (b) (4) Since the efficacy information is not integrated, Takeda does not plan to include a Clinical Summary of Efficacy (2.7.3) in the NDA resubmission but will rely on the data included in the individual clinical study reports. Is the Agency agreeable to this approach?

FDA Preliminary Response: (b) (4) **we agree with your plan to update the efficacy section of the alogliptin package insert with data from completed study MET-302. Since the efficacy information is not integrated, we agree with your plan to not include a Clinical Summary of Efficacy (2.7.3) in the resubmission.**

Question 9: Due to the fact that labeling negotiations had initiated under the previous review cycle and there are still some aspects other than safety that need to be discussed, Takeda proposes not to include Structured Product Labeling (SPL) in the NDA resubmissions. Takeda will provide the package insert information in SPL format once labeling language has been agreed upon by both Takeda and the Agency. Is this acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable.

Question 10: Does the Agency agree with the process for enhanced monitoring of postmarketing liver-related cases?

FDA Preliminary Response: Yes, we agree with the process for enhanced monitoring of postmarketing liver-related cases.

Question 11: During the course of the review of the NDA resubmissions, spontaneous reports related to hepatic safety may be received. Takeda will continue to expedite these reports to the INDs and NDAs, as previously agreed. However, in an effort to provide a meaningful adjudication of these cases, Takeda often needs adequate time to gather relevant information for an individual postmarketing case. Therefore, the LSEC will review new cases on a monthly basis, and their assessments will be subsequently submitted to the Agency. Is this approach reasonable to the Agency?

FDA Preliminary Response: Yes, your approach is reasonable. However, additional information may be requested as needed.

Question 12: If during the course of the review of the NDA resubmissions, there is striking disagreement between the Agency and the LSEC on a particular liver safety case(s), would the Agency consider discussing the case(s) with the LSEC (and Takeda)?

FDA Preliminary Response: Yes, we may consider discussing case(s) with you and the LSEC. However, the purpose of such discussion would be to share information to ensure that both you and the Agency have all currently available data to aid decision-making. The

objective of the meeting would not be to obtain a consensus of opinion on liver case(s) or to discuss upcoming regulatory decision(s).

Question 13: Is the Agency agreeable to discussing how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End of Review meeting?

FDA Preliminary Response: Yes, we may discuss how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End-of-Review meeting.

Question 14: In the 25 April 2012 Complete Response Letter, there are questions related to the alogliptin pediatric program. Takeda is currently planning on initiating the phase 3 program in early 2013 due to Pediatric Committee requirements. In order to incorporate the Agency's feedback into the studies before they are started, Takeda plans to submit responses to the pediatric questions in an IND Amendment. Is this proposal acceptable?

FDA Preliminary Response: You may submit responses to the pediatric questions in an IND amendment. However, please note that a pediatric postmarketing study requirement cannot be issued until after an NDA is approved. Please also submit relevant information to the NDA.

Additional Comment:
Please explain whether or not you plan to (b) (4)

could possibly offset the potential liver liability.

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/s/

MEHREEN HAI
06/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING REQUEST GRANTED

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to your correspondence dated April 27, 2012, requesting an End-of-Review meeting to discuss the deficiencies described in our Complete Response letter dated April 25, 2012, and to discuss actions to be taken to address these deficiencies. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date:	June 29, 2012
Time:	2:00 – 3:00 PM
Location:	10903 New Hampshire Avenue White Oak Building 22 Silver Spring, Maryland 20903

CDER participants (tentative):

<u>Office of New Drugs</u>

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Valerie Pratt, M.D.	Clinical Reviewer, DMEP

Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Biostatistics Reviewer, Division of Biometrics II
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII
Eugenio Andraca-Carrera, Ph.D.	Biostatistics Reviewer, Division of Biometrics VII
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Amy Egan, M.D., M.P.H.	Deputy Director for Safety, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

Office of Surveillance and Epidemiology

Leonard Seeff, M.D.	Hepatologist
John Senior, M.D.	Hepatologist
Margarita Tossa, M.S.	Safety Regulatory Project Manager

Please e-mail me any updates to your attendees at mehreen.hai@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Mehreen Hai: x65073;
Lena Staunton: x67522.

Submit background information for the meeting (one electronic copy to the application and 25 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **May 30, 2012**, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

Mehreen Hai
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3391
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MEHREEN HAI
05/09/2012

MEMORANDUM OF TELECON

DATE: **April 16, 2012 (12:00 – 1:00 P.M. EST)**

APPLICATION NUMBER: **Pending NDA 022271 and NDA 022426**

DRUG NAME: **Alogliptin tablets**
Alogliptin and pioglitazone fixed-dose combination tablets

BETWEEN:

Takeda Global Research and Development Center, Inc.
Sandra Cosner, RPh - Associate Director, Regulatory Affairs
Penny Fleck, MT - Senior Director, Clinical Science
Thomas Harris, RPh - Vice President, Regulatory Affairs
Qais Mekki, MD, PhD - Vice President, Pharmacovigilance
Azmi Nabulsi, MD - President, Takeda Global Research and Development
Neila Smith, MD - Executive Medical Director, Pharmacovigilance
Thomas Strack, MD - Therapeutic Area Head, Diabetes, Pharmaceutical Drug Development
Allison Villinski, MS - Director, Regulatory Affairs

External hepatology consultants for Takeda:

(b) (4)

AND

Office of New Drugs
Curtis Rosebraugh, MD - Director, Office of Drug Evaluation II
Mary Parks, MD - Director, Division of Metabolism and Endocrinology Products (DMEP)
Hylton Joffe, MD, M.M.Sc. - Diabetes Team Leader, DMEP
Valerie Pratt, MD - Clinical Reviewer, DMEP
Mehreen Hai, PhD - Regulatory Project Manager, DMEP

Office of Surveillance and Epidemiology
Leonard Seeff, MD - Hepatologist
John Senior, MD - Hepatologist
Allen Brinker, MD, MS - Medical Team Leader, Division of Pharmacovigilance I (DPV I)
Margarita Tossa, MS - Safety Regulatory Project Manager

SUBJECT: Discussion regarding cases of hepatic injury associated with use of alogliptin

Background

Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that has been developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Alogliptin is a fourth-in-class new molecular entity. The NDA for alogliptin was submitted on December 27, 2007, and was issued a Complete Response letter on June 26, 2009. Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 021073 (Tradename: Actos). The NDA for alogliptin-pioglitazone fixed-dose combination tablets was submitted on September 19, 2008, and was issued a Complete Response letter on September 2, 2009.

Takeda resubmitted both NDAs on July 25, 2011. On November 16, 2011, the review clock was extended by 3 months based on liver analyses submitted at our request, resulting in a PDUFA goal date of April 25, 2012.

During the review of the resubmissions, several pre- and post-marketing cases of liver injury associated with the use of alogliptin were identified. These cases were adjudicated to determine relatedness to alogliptin by the FDA hepatologists in the Office of Surveillance and Epidemiology, Dr. Leonard Seeff and Dr. John Senior, and also by Takeda's independent consultants (b) (4)

While near-consensus was reached for most cases by these four hepatologists, one case in particular, TCI2011A04573, was adjudicated differently. This teleconference was arranged to allow discussion between the hepatologists regarding this case and, if needed, any additional cases.

Teleconference

After a brief introduction by Dr. Thomas Harris from Takeda, the four hepatologists discussed case TCI2011A04573. Dr. Seeff's opinion was that this case was probably related to the drug, while (b) (4) considered it unlikely to be drug-related, and (b) (4) considered it to be possibly related to the drug (b) (4) considered this case to be more likely due to autoimmune hepatitis, noting the coexisting autoimmune thyroid disease and the rebound in the liver test elevations with tapering of the glucocorticoid dose. Dr. Seeff remained unconvinced given the negative autoimmune serologies and the development of liver injury coincident with the use of alogliptin. Dr. Joffe also questioned whether the rebound convincingly is related to the glucocorticoid taper as the liver tests improved despite a continued reduction in the glucocorticoid dose. There was also a brief discussion of six other cases: TCI2011A03640, TCI2010A05612, TCI2011A04039, TCI2011A06837, TCI2012A01179 and TCI2011A06481, with Dr. Seeff noting that he and (b) (4) are better aligned in their assessments for these cases than case TC2011A04573. At the end of the teleconference call, Dr. Parks stated that FDA is concerned with the signal for hepatotoxicity with alogliptin.

Memo prepared by: Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Hai, Mehreen

From: Hai, Mehreen
Sent: Wednesday, April 18, 2012 2:44 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info Request for NDA 22271 and 22426

Hi Sandy,
We have the following information request for the alogliptin NDAs:

Please refer to your November 7, 2011, response to our October 24, 2011, information request.

Table 7 in your November 7, 2011, submission (ongoing Study 402 alone) shows that 18 alogliptin-treated patients and 13 placebo-treated patients had a baseline ALT >3x ULN.
Table 8 in your November 7, 2011, submission (all completed phase 2/3 trials, including the Japanese phase 2/3 trials and ongoing Study 402) shows that 30 alogliptin-treated patients and 10 comparator-treated patients had a baseline ALT >3x ULN.

Please clarify the following:
1. Did all controlled phase 2/3 trials have ALT exclusion criteria except for Study 402? Were there any ALT exclusion criteria for the controlled phase 2/3 Japanese studies that were included in Table 8?
2. Clarify why the number of comparator-treated patients with baseline ALT >3x ULN is higher in Study 402 alone (n=13) compared to the pooled phase 2/3 database that includes Study 402 (n=10).
3. Did all the patients with baseline ALT >3x ULN in Tables 7 and 8 receive randomized study medication and have at least one post-baseline ALT value or do these tallies include some patients who were excluded from the trial?

Please respond as soon as possible.
Thanks!

Mehreen Hai, Ph.D.
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/s/

MEHREEN HAI
04/18/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Wednesday, April 18, 2012 3:18 PM
To: 'Cosner, Sandra (TGRD)'
Subject: RE: Info Request for NDA 22271 and 22426

Hi Sandy,
Please add the following two items to the information request below:

1. Clarify whether the patients who developed treatment-emergent ALT >10x ULN in the controlled phase 2/3 database all had ALT >3x ULN at baseline. What happened to ALT during the randomized treatment period for those with ALT >3x ULN at baseline?

2. At the teleconference call, we requested an estimate of patient-year exposures anticipated for Study 402 at the time 1.3 is met. When do you anticipate submitting this information?

Thanks!

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Fax: 301-796-9712

From: Hai, Mehreen
Sent: Wednesday, April 18, 2012 2:44 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info Request for NDA 22271 and 22426

Hi Sandy,
We have the following information request for the alogliptin NDAs:

Please refer to your November 7, 2011, response to our October 24, 2011, information request.

Table 7 in your November 7, 2011, submission (ongoing Study 402 alone) shows that 18 alogliptin-treated patients and 13 placebo-treated patients had a baseline ALT >3x ULN.
Table 8 in your November 7, 2011, submission (all completed phase 2/3 trials, including the Japanese phase 2/3 trials and ongoing Study 402) shows that 30 alogliptin-treated patients and 10 comparator-treated patients had a baseline ALT >3x ULN.

Please clarify the following:
1. Did all controlled phase 2/3 trials have ALT exclusion criteria except for Study 402? Were there any ALT exclusion criteria for the controlled phase 2/3 Japanese studies that were included in Table 8?
2. Clarify why the number of comparator-treated patients with baseline ALT >3x ULN is higher in Study 402 alone (n=13) compared to the pooled phase 2/3 database that includes Study 402 (n=10).
3. Did all the patients with baseline ALT >3x ULN in Tables 7 and 8 receive randomized study medication and have at least one post-baseline ALT value or do these tallies include some patients who were excluded from the trial?

Please respond as soon as possible.
Thanks!

Mehreen Hai, Ph.D.

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/s/

MEHREEN HAI
04/18/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Monday, April 02, 2012 4:01 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info requests for NDA 22271 and 22416

Hi Sandy,
We have the following information requests for the alogliptin NDAs:

Regarding your cardiovascular trial (EXAMINE):

1. Have you completed enrollment in EXAMINE? Please provide 'n' for alogliptin and control who have had at least 6 months of exposure to treatment.
2. If answer to Q1 is 'no', how many patients have been randomized to alogliptin and control at present? How many of these have had at least 6 months of exposure to treatment?
3. If answer to Q1 is 'no', when do you anticipate completion of enrollment? And from this estimate, when do you anticipate all 5400 patients planned for study to have had at least 6 months of exposure to treatment?

Regarding the follow-up report that was submitted on March 30, 2012, for liver-related case TCI2012A01179:

4. The recent update for case TCI2012A01179 requires additional data to determine if the patient had acute hepatitis E infection. Please inquire of the reporting physician(s) whether there are stored, frozen serum samples available. We are specifically looking for HEV IgM and IgG antibodies. Serial tests of these antibodies and HEV RNA by PCR will be extremely useful.

5. Please also inquire of the reporting physician(s) whether an extensive history was taken of the patient's recent travels, exposure to animals or eating wild boar, and provide any such report.

Regarding liver-related case TCI2011A06481:

6. For postmarketing liver case TCI2011A06481, clarify whether there are hepatitis E test results available. If this patient did not undergo testing for hepatitis E, are there blood samples available that can be tested?

Thanks!

Mehreen Hai, Ph.D.
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MEHREEN HAI
04/02/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Monday, March 26, 2012 8:22 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Carton and Container Label comments

Attachments: Oseni (alogliptin and pioglitazone) CC Label Comments.pdf

Hi Sandy,
Please find attached our comments on the carton and container labels for NDA 22-426 (alogliptin-pioglitazone).
Let me know if you have any questions.

Oseni (alogliptin and pioglita...

Mehreen Hai, Ph.D.
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A. General Comments (All Container Labels and Carton Labeling; All Strengths)

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all factors, including typography, layout, contrast and other pertinent features as per 21 CFR 201.10(g)(2).

2. Ensure that sufficient number of Medication Guides is provided with the product such that a dispenser can provide one Medication Guide with each new prescription. This is to comply with the requirement 21 CFR 208.24.

3. Replace the slash "/" used between the active ingredients in the established name (alogliptin/pioglitazone) with the word "and." The established name should read "(alogliptin and pioglitazone) tablets".

B. Container Labels (Bottles)

1. All Strengths; All Bottle Sizes (7-count, 30-count, 90-count, 500-count)

   a. Remove [redacted] (b) (4)

   b. Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxxx-XXX-xx). Pharmacists use the middle portion of the NDC number to ensure the correct product is dispensed.

   c. Remove the statements [redacted] (b) (4) to reduce clutter and allow increasing of the font size and improving readability of other important information on the label.

2. All Strengths; 30-count, 90-count, and 500-count Bottle Sizes

   a. Relocate the statement that reads "Each film-coated tablet contains…" from the Principal Display Panel (PDP) to the side panel because it crowds the PDP. Only the most important information such as product proprietary name, established name, dosage form, and strength should be on the PDP.

3. All bottle sizes for the 12.5 mg/15 mg and 25 mg/15 mg strengths

   a. Revise the color scheme used to highlight the strength statement of the 12.5 mg/15 mg [redacted] (b) (4) and the 25 mg/15 mg [redacted] (b) (4)

4. All bottle sizes for the 12.5 mg/45 mg and 25 mg/45 mg strengths

   a. Revise the color scheme used to highlight the strength statement of the 12.5 mg/45 mg (b) (4) and the 25 mg/45 mg (b) (4)

5. All bottle sizes for the 12.5 mg/30 mg strength

   a. Revise the color font of the 12.5 mg/30 mg strength or the boxing used for highlighting the strength (b) (4) to provide adequate contrast to increase readability of the strength. (b) (4)

6. All bottle sizes for the 25 mg/30 mg strength

   a. Revise the color scheme of the 25 mg/30 mg strength (b) (4)

C. Blister Card Container Labels (All Strengths)

1. Refer to previous comments B.3. to B.6. regarding your color scheme for the different strengths and apply accordingly.

2. Revise the strength statement "XX mg/XX mg to read "XX mg/XX mg per tablet." For example, "12.5 mg/45 mg" to read 12.5 mg/45 mg per tablet"

3. Include a statement which communicates that the blister pack is not child resistant and to keep out of reach of children.

4. (b) (4)

5. Revise the day designation on the inner card (i.e. Mon, Tues., etc.) (b) (4)

D. Carton Labeling (Blister Cartons; All Strengths)

1. Refer to previous comments B.3. to B.6. regarding your color scheme for the different strengths and apply accordingly.

2. Revise the strength statement "XX mg/XX mg to read "XX mg/XX mg per tablet." For example, "12.5 mg/45 mg" to read 12.5 mg/45 mg per tablet"

3. Revise the statement (b) (4)

4. Relocate the net quantity statement to the principal display panel. Ensure the net quantity is located away from the product strength.

E. Carton Labeling (7-count sample bottles; All Strengths)

1. Refer to previous comments B.3. to B.6. regarding your color scheme for the different strengths and apply accordingly.

2. Revise the strength statement "XX mg/XX mg to read "XX mg/XX mg per tablet." For example, "12.5 mg/45 mg" to read 12.5 mg/45 mg per tablet"

3. Revise the statement (b) (4)

F. Insert Labeling

1. Dosage and Administration Section 2.1

   a. Replace the slash "/" used between the active ingredients in the established name (alogliptin/pioglitazone) with the word "and." The established name should read "(alogliptin and pioglitazone) tablets".

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/s/

MEHREEN HAI
03/26/2012

Hai, Mehreen

From	Hai, Mehreen
Sent	Friday, March 30, 2012 10:23 PM
To	'Cosner, Sandra (TGRD)'
Subject	RE: Info request for NDA 22271 and 22426

Sandy,
Thank you, we received your submission today.

We have the the following additional information requests for the alogliptin NDAs:

1. Have you been able to obtain any further information regarding postmarketing case TCI2011A06369?

2. Please provide us with the assessments from (b) (4) for postmarketing case TCI2011A06369 and TCI2011A06481. If these assessments have been previously submitted to the alogliptin NDA, please point us to their location.

Thanks!

Mehreen Hai, Ph.D.
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Division of Metabolism & Endocrinology Products
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mehreen.hai@fda.hhs.gov
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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Friday, March 30, 2012 1:15 PM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: RE: Info request for NDA 22271 and 22426

Hi Mehreen,
I wanted to give you a heads up that we are responding to this Information Request today. Please let me know if you would like for me to email you a copy in addition to the submission.
Thanks,
Sandy

Sandra D Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc
Office (224) 554-1957
Mobile (b) (6)
Fax (224) 554-7870
Email: sandra cosner@takeda com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs gov]
Sent: Tuesday, March 27, 2012 9:13 PM

To: Cosner, Sandra (TGRD)
Subject: Info request for NDA 22271 and 22426

Hi Sandy,
Please see below the information request for the alogliptin NDAs, that Dr. Parks mentioned during our conversation this afternoon, regarding the liver case that was reported in the safety report submitted on Thursday, March 22.

1. Please obtain medical/hospital records to determine if patient was ever febrile or complained of abdominal pain at presentation of this event.

2. Please obtain a complete report from the pathologist reading the liver biopsy results.

3. Please inquire if patient has been tested for Hepatitis E.

Thanks!

Mehreen Hai, Ph.D.
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MEHREEN HAI
03/30/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Tuesday, March 27, 2012 10:13 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info request for NDA 22271 and 22426

Hi Sandy,
Please see below the information request for the alogliptin NDAs, that Dr. Parks mentioned during our conversation this afternoon, regarding the liver case that was reported in the safety report submitted on Thursday, March 22.

1. Please obtain medical/hospital records to determine if patient was ever febrile or complained of abdominal pain at presentation of this event.

2. Please obtain a complete report from the pathologist reading the liver biopsy results.

3. Please inquire if patient has been tested for Hepatitis E.

Thanks!

Mehreen Hai, Ph.D.
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MEHREEN HAI
03/27/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Tuesday, March 20, 2012 11:03 AM
To: 'Cosner, Sandra (TGRD)'
Subject: Info request for NDA 22271

Hi Sandy,
We have the following information request for the alogliptin NDAs:

In your third Periodic Safety Update Report you state that the cumulative patient exposure to aloglipin (from approval through 15 October 2011) in the Japanese postmarketing setting is estimated to be 117,359 patient-years. The corresponding estimate for the alogliptin-pioglitazone fixed-dose combination product is 7,215 patient-years. Please clarify how you calculated these patient-year exposures.

Also, we had estimated that we would get our labeling comments back to you this week, but we will likely be delayed again to sometime next week, since our senior reviewers/management are currently engaged in internal discussion, and in the process of finalizing their reviews.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
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MEHREEN HAI
03/20/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Thursday, March 15, 2012 10:13 AM
To: 'Cosner, Sandra (TGRD)'
Subject: Information requests for NDA 22271

Hi Sandy,
We have the following information requests for the alogliptin NDAs:

1. The narratives for the following liver cases contain insufficient information and some of them are poorly written with apparent discrepancies within the narrative. Please provide revised narratives that are thorough and clear. For each case that you do not attribute to alogliptin, state what you believe to be the alternative etiology:

OPI-002/831-2508
OPI-001/395-3054
012/961-3006
012/961-2501
TCI2011A02923 (insufficient information to determine whether the cause is hepatitis C or alogliptin-related hepatotoxicity).

2. In PSUR 3, the table with cumulative, unlisted serious adverse drug reactions shows one case of red blood cell aplasia. Please provide a narrative.

3. As of the May 31, 2011 cutoff date, clarify the extent of patient exposure in Study 012.

4. Provide narratives (or point us to the location within your submissions) for the alogliptin-treated patients in the Japanese phase 2/3 trials who discontinued due to drug hypersensitivity, dermatitis bullous, rash, toxic skin eruption and face oedema.

5. You table of treatment-emergent adverse events for the pool of phase 2/3 controlled studies shows that 5 patients reported a serious adverse event of pancreatitis. However, your table of narratives for pancreatitis show only 4 patients with serious pancreatitis. Please clarify the apparent discrepancy.

6. Please submit the narrative for the serious adverse event of drug hypersensitivity reported in an alogliptin-treated patient in your Japanese controlled phase 2/3 trial.

7. Please submit narratives for the alogliptin-treated patients in your phase 2/3 program (including Japanese studies and ongoing Study 402) who had adverse events that coded to the preferred terms of angioedema (n=1), face oedema (n=6), swelling face (n=3), swollen tongue (n=1), and tongue oedema (n=1).

8. Please submit narratives for the alogliptin-treated patients in your phase 2/3 program (including Japanese studies and ongoing Study 402) who had adverse events that coded to the preferred terms of dermatitis exfoliative and exfoliative rash.

Thanks!

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/s/

MEHREEN HAI
03/15/2012

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)"
Subject: Info Requests for NDA 22271 and 22426
Date: Thursday, March 01, 2012 11:52:00 AM

Hi Sandy,
We have the following information requests related to the alogliptin and alogliptin-pioglitazone NDAs:

Clinical:

1) Please submit a summary of your planned studies and ongoing studies for alogliptin, together with their status and estimated completion dates.

2) Please submit the first PSUR for your alogliptin products approved in Japan.

Biopharmaceutics:

3) Your language of the proposed specification (b) (4) (Q) of the labeled amount is dissolved in 15 minutes" needs to be clarified as "Q = (b) (4) of the labeled amount dissolved in 15 minute". (b) (4) and "Q "are not same.

4) What is the pH of your dissolution medium?

Thanks!

Mehreen Hai, Ph.D.
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MEHREEN HAI
03/01/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Comments re. REMS for NDA 022426
Date:	Thursday, March 01, 2012 12:31:00 PM
Attachments:	(b) (4) REMS document-FDA edits-1March2012.doc (b) (4) REMS comments-1March2012.pdf

Hi Sandy,
Please find attached our comments/edits regarding the the alogliptin-pioglitazone REMS that you submitted on September 12, 2011.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
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5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MEHREEN HAI
03/01/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Labeling comments for NDA 22271 and 22426 - Round 2
Date:	Friday, February 17, 2012 8:27:00 PM
Attachments:	Nesina-PI-FDA EDITS-17February2012.doc OSENI-PI-FDA EDITS-17February2012.doc FDA Response to Takeda re. Section 13.1 (2-17-12).pdf

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Hi Sandy,
Please find attached our second round of edits to the package inserts (PI) for alogliptin and alogliptin-pioglitazone, incorporating comments from all disciplines. The edits to the alogliptin-pioglitazone PI are minimal, as we have focused on the alogliptin PI during this round. We have requested that you incorporate the relevant changes in the alogliptin PI to the alogliptin-pioglitazone PI as well. We remind you once again that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Once again, please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you.

Please also find attached a document containing our response to your document explaining the rationale for your edits made in Paragraph 2 of Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), that you emailed me on February 9, 2012, along with your first round of edits to the alogliptin and alogliptin-pioglitazone package inserts.

We request that you respond with your edits and comments by **Monday, February 27, 2012**.
Please confirm receipt of this email, and let me know if you have any questions.
Thanks!

Mehreen Hai, Ph.D.
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FDA Response to Takeda's document explaining the rationale for the edits made in Paragraph 2 of Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), emailed by Sandra Cosner (Takeda) to Mehreen Hai (FDA) on February 9, 2012

The Division and the Executive CAC considered your arguments that no carcinogenic effect of alogliptin was observed in the two-year rat bioassay. We recognize that these arguments were made in the original study report from (b) (4) in 2007, which were reviewed by the Division and thoroughly discussed with the Executive CAC at that time. We disagreed then and we continue to disagree with the interpretation that the C-cell findings in rats, particularly in male rats, were a spurious finding and not related to alogliptin. Based on the multiple to clinical exposure of the NOAEL, we agree that the finding in rats does not pose a substantial carcinogenic risk to human subjects under conditions of clinical use. This is explicitly stated in the proposed label. However, statistically significant tumor findings in rodent bioassays are nevertheless described in drug labels and, when supportive data are available, the findings are put in context regarding the human relevance of the finding.

Specific responses to your arguments are as follows:

Takeda Comments 1 & 2:

- Statistical analyses of hyperplasia, adenoma, or carcinoma separately only showed significance in the incidence of adenomas in males at the mid-dose (400 mg/kg/day) and not at the high-dose (800 mg/kg/day).
- No statistical significance was noted in the combined incidence of hyperplasia, adenoma, and carcinoma.

FDA Response: Hyperplasia, adenoma, and carcinoma of thyroid C-cells are considered a continuum of histological changes with preneoplastic lesions often proceeding to benign and then occasionally to malignant neoplasms. Consistent with McConnell's publication (1986), the incidence of C-cell benign and malignant tumors are combined for statistical comparisons. Hyperplasia is excluded from analysis because this lesion is not a neoplasm and hyperplasia is not typically diagnosed when neoplasms are present in the same organ. Statistical analysis demonstrates that the combined incidence of C-cell adenoma and carcinoma increased at the mid and high doses of alogliptin in male rats with statistical significance by trend and pair-wise comparison. This outcome will not change.

Takeda Comment 3:

- The incidence of adenomas in the control group of this study was lower than that seen in the Historical Control (HC) data from the testing laboratory. And, although the percentage of thyroid c-cell adenomas in alogliptin-treated males was slightly higher than the HC, 16.7% and 18.3% (400 and 800 mg/kg/day, respectively) compared to 15.4%, the incidences were essentially equivalent (10/65 HC versus 10 or 11/60 alogliptin).

<u>FDA Response</u>: A dose response was evident in male animals across the dose range for the combined adenoma/carcinoma C-cell findings and, as you note, the incidence exceeded historical controls at the high dose. If the observed incidences were indeed random variation around a historical mean, the probability that a dose response is observed in the relevant endpoint is very low. The increased incidence in females dosed with alogliptin but without a clear dose-dependence may in fact reflect a plateau in response; however, because statistical significance was not evident in females, the Executive CAC recommended against including this finding in the drug label.

<u>Takeda comment 4</u>:

- The dose response for both adenomas and precursory hyperplastic lesions in the thyroid c-cell was weak.

<u>FDA Response</u>: See response to Comments 1, 2 & 3, above.

<u>Takeda comment 5</u>:

- There is no evidence of mutagenicity in any of the nonclinical assays with alogliptin.

<u>FDA Response</u>: We agree that genotoxicity is not relevant to this case. Rather, we interpret this finding as evidence of a non-genotoxic carcinogenic response to alogliptin. Findings of C-cell tumors in rats have been observed with direct acting GLP1 agonists, suggesting a biologically plausible mechanism for the effects observed with alogliptin, which indirectly increases GLP1.

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/s/

MEHREEN HAI
02/17/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Info request for NDA 022271 and 022426
Date:	Wednesday, February 15, 2012 12:06:00 PM

Hi Sandy,
We have the following information request for the alogliptin NDAs:

In the November 7, 2011 submission to NDAs 022271 and 022426, in the During Treatment column of Table 8, you list 2, 8, 11, and 21 All Alogliptin subjects with ALT > 20x, >10x, >8x, and >5x ULN, respectively, and 6 All Comparator subjects with ALT >5x or >8x ULN. Within 1 week, submit narratives for these cases that are sorted by the degree of ALT elevation and treatment group. Submit these narratives to NDAs 022271, 022426, and 203414.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
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MEHREEN HAI
02/15/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Labeling comments for NDA 22271 and 22426
Date:	Thursday, January 26, 2012 3:18:00 PM
Attachments:	Nesina-PI-FDA EDITS-26January2012.doc (b) (4) -PI-FDA EDITS-26January2012.doc

Hi Sandy,
Please find attached our first round of edits to the package inserts for alogliptin and alogliptin-pioglitazone, incorporating comments from CMC, Pharm/Tox, Statistics and Clinical Pharmacology. Clinical comments are still pending, and will be provided to you once the clinical review is complete. We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you.

Please confirm receipt of this email, and let me know if you have any questions. Once you've had a chance to review our comments, please let me know when we can expect to receive your response.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

77 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEHREEN HAI
01/26/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Info request for alogliptin
Date:	Friday, January 13, 2012 3:56:00 PM

Hi Sandy,
We have the following information request regarding the three liver-related safety reports that were submitted to IND 69707 (alogliptin), IND 73193 (alogliptin-pioglitazone) and IND 101628 (alogliptin-metformin) on January 10, 2012:

Please let us know when you expect to have additional details on these three cases. Please also have your liver experts review these cases and submit these cases (with follow-up/additional information), together with the assessment from your two liver experts, to the pending NDAs for these respective products. While the alogliptin NDA is under review, please also submit to the NDAs all future alogliptin liver events that would ordinarily come in only to the INDs.

Also, please submit to your NDAs the most recent PSUR for your alogliptin products approved in Japan.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
01/13/2012

Hai, Mehreen

From: Suggs, Courtney
Sent: Friday, January 13, 2012 7:38 AM
To: Hai, Mehreen
Cc: Mathis, Lisa; Addy, Rosemary; Lee, Catherine S.; Parks, Mary H
Subject: NDA 22426 Alogliptin+Pioglitazone Amended Confirmation of PeRC Review

Attachments: 1_Pediatric_Record.pdf; 1_Pediatric_Record.pdf

Hi Mehreen,

The email serves as confirmation of the review for the alogliptin+pioglitazone, NDA 22426, product conducted by the PeRC PREA Subcommittee on January 11, 2012.

The Division presented a full waiver in patients ages birth to 18 years of age for the indication of treatment of type 2 diabetes mellitus.

The PeRC agreed with the Division to grant a full waiver from birth to 18 years of age based on evidence strongly suggesting that the product would be unsafe in this pediatric population based on the risk of bladder cancer and fractures associated with pioglitazone use.

- The PeRC recommends strengthening the label language in Section 8.4 to note the product should not be used in pediatric patients due to risk of adverse events.

The amended pediatric record is attached for alogliptin+pioglitazone.

1_Pediatric_Record .pdf (57 KB)...

Thanks,

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Suggs, Courtney
Sent: Wednesday, January 11, 2012 12:39 PM
To: Hai, Mehreen
Cc: Mathis, Lisa; Addy, Rosemary; Greeley, George; Lee, Catherine S.
Subject: NDA 22426 Alogliptin+Pioglitazone

Hi Mehreen,

The email serves as confirmation of the review for the alogliptin+pioglitazone, NDA 22426, product conducted by the PeRC PREA Subcommittee on January 11, 2012.

The Division presented a full waiver in patients ages birth to 18 years of age for the indication of treatment of type 2 diabetes mellitus.

The PeRC agreed with the Division to grant a full waiver from birth to 18 years of age based on evidence strongly suggesting that the product would be unsafe in this pediatric population based on the risk of bladder cancer and fractures associated with pioglitazone use.

The amended pediatric record is attached for alogliptin+pioglitazone.

1_Pediatric_Record .pdf (60 KB)...

Thanks,

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022426

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

Attention: Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated September 19, 2008, received September 22, 2008 and to your Class 2 Resubmission dated July 25, 2011, received July 25, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Pioglitazone Tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg.

We also refer to your October 18, 2011, correspondence, received October 19, 2011, requesting review of your proposed proprietary name, Oseni. We have completed our review of the proposed proprietary name, Oseni, and have concluded that it is acceptable.

The proposed proprietary name, Oseni, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 18, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Mehreen Hai at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/23/2011

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Information request for alogliptin
Date:	Wednesday, December 14, 2011 12:04:00 PM
Attachments:	IR for NDA 22271.pdf

Hi Sandy,
Please find attached an information request for NDAs 22271 and 22426.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Information request concerning elderly study 303:

The inspection findings are pending for site #3018 (Lagrosa) involved in study SYR-322_303. Therefore, for this study, please analyze the following without site #3018 and complete the table below:

- HbA1c change from baseline at week 52 for A) FAS/LOCF; B) PPS/LOCF
- HbA1c ≤ 7.0 at week 52 for FAS/LOCF (responder analysis).

Please also calculate two-sided 95% CI's of the treatment arm comparisons and complete the table below. We are using Tables 11.b and 11.h from the clinical report for Study 303 as models for this table.

Study 303: HbA1c change from baseline at week 52

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value
1. HbA1c change from baseline at week 52					
A. FAS/LOCF					
Alogliptin					
Glipizide					
B. PPS/LOCF					
Alogliptin					
Glipizide					
2. HbA1c ≤ 7.0; Week 52; FAS/LOCF					
		n (%)		Odds Ratio[2] (95% CI)	
Alogliptin					
Glipizide					

Notes:

[1] Analysis for HbA1c change from baseline: The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary analysis of covariance model, with treatment, study schedule and geographic region as class variables, and baseline HbA1c as a covariate.

[2] Analysis for HbA1c ≤ 7.0: The logistic regression model included effects for treatment, geographic region, study schedule and baseline HbA1c.

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/s/

MEHREEN HAI
12/14/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, December 07, 2011 1:35 PM
To: 'scosner@tgrd.com'
Cc: Hai, Mehreen; Sharma, Khushboo
Subject: Re: NDA 22426 Information request-Dec.7, 2011

Dear Ms. Cosner,

Please refer to your NDA submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Alogliptin/Pioglitazone Fixed Dose Combination (FDC) Tablets. We also refer to your amendment dated July 27, 2011.

We have the following comments and recommendation:

Your revised dissolution method using Apparatus 2 with PEAK vessels at 50 rpm is acceptable. However, based on the overall dissolution profile data using Apparatus 2 with PEAK vessels at 50 rpm, the Agency recommends the following dissolution testing conditions and acceptance criteria for SYR-322-4833 Tablets (e.g., for both alogliptin and pioglitazone).

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

In the communication dated July 27, 2011 (S-031), You proposed as a second option, to further evaluate at both 15 and 30 minutes sampling times the dissolution of pioglitazone from SYR-322-4833 tablets for the release and stability batches manufactured during the first year post approval date, while maintaining the acceptance criterion of Q= (b) (4) in 30 minutes for pioglitazone on an interim basis. Also,

a. In the course of this one year post-approval evaluation period, you will collect dissolution data from multiple commercial lots at release and also from stability studies at several intervals up to 24 months.

b. At the end of the one year period, if the additional dissolution data clearly support that (b) (4) you have committed to implement a revised (b) (4) acceptance criterion of Q= (b) (4) in 15 minutes for pioglitazone. This change will be reported in a supplement to the NDA.

c. However, if the additional data do not support that the dissolution acceptance criterion for pioglitazone be (b) (4) Q= (b) (4) in 15 minutes, you will report in a supplement to the NDA these additional dissolution data and the justification for keeping Q= (b) (4) at 30 minutes as the final dissolution acceptance criterion for pioglitazone.

Your second option, as outlined above, is acceptable by the Agency and the Agency, hereby, requests you to agree to their proposed second option by submitting a formal amendment with the agreement referenced above.

Please acknowledge the receipt.
Let me know if you have any question or concern

Swati Patwardhan

Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
12/08/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: RE: Nov 16 Information Request for NDA 22-271
Date: Monday, December 05, 2011 12:47:29 PM

Sandy,
Thanks for the clarification.
To clarify something from our end, please submit (b) (4) report, and highlight where his assessment differs from (b) (4)

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Monday, December 05, 2011 10:22 AM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: RE: Nov 16 Information Request for NDA 22-271

Hi Mehreen,
I apologize for any confusion. When I had sent you the email on Thursday I was not aware we would receive (b) (4) report earlier than expected. Then we received it Friday morning and therefore submitted on that same day. This is the same submission I said we would submit the week of Dec. 12, again, sorry for the confusion.

We will work on your additional request below and get back to you soon.
Thanks,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Office (224) 554-1957
Mobile (b) (6)
Fax (224) 554-7870
Email: sandra.cosner@takeda.com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, December 02, 2011 8:58 PM
To: Cosner, Sandra (TGRD)
Subject: RE: Nov 16 Information Request for NDA 22-271

Thanks, Sandy. I'm a bit confused - you say in your email below that you will be submitting (b) (4) evaluation around December 16. Is this different from what you submiited to the NDAs today?

Also, we request that you provide (b) (4) evaluation for the cases in which his conclusions differed from (b) (4) conclusions.

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, December 01, 2011 11:11 AM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: Nov 16 Information Request for NDA 22-271

Dear Mehreen-

I wanted to quickly follow up on the Agency's November 16th information request regarding the receipt of additional information requested from (b) (4) Since the Agency's request requires (b) (4) to evaluate information from the ongoing CV outcomes trial (Study 402; EXAMINE), Takeda has unblinded (b) (4) per internal Standard Operating Procedures. (b) (4) has received all of the unblinded information from the submission provided to the Agency on November 7th and is currently evaluating the data. Takeda expects to receive his expert opinion and submit it to the FDA by no later than the week of December 12th.

In the spirit of transparency, Takeda also wanted to inform the FDA that an additional hepatologist, (b) (4) received the serious, non-serious and post-marketing cases (and these only) in a blinded fashion following the Agency's October 24th request for information. Takeda has received (b) (4) evaluation of the blinded cases and this evaluation is generally aligned with the information included in Appendix 1 of (b) (4) review provided to FDA on November 7th. Takeda, therefore, is not planning on including this report in the mid-December submission. Takeda is also not requesting additional feedback from (b) (4) in an effort to minimize the number of individuals unblinded to alogliptin data, but is instead focusing on providing the Agency with (b) (4) overall interpretation per your request in an expedited fashion.

If you should have any questions please feel free to contact me. Thanks!

Kindest Regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Mobile (b) (6)
Fax (224) 554-3646
Email: scosner@tgrd.com

###
The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and is the property of Takeda. Unauthorized use, disclosure, or copying of this communication, or any part thereof, is strictly prohibited and may be unlawful. If you received this communication in error, please notify me immediately by

return e-mail and destroy this communication and all copies thereof, including all attachments.

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/s/

MEHREEN HAI
12/05/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request
Date: Wednesday, November 16, 2011 2:43:24 PM

Hi Sandy,
We have the following information request for NDA 22271 and 22426:

In reference to the liver-related information that you submitted on November 7, 2011, and more specifically the External Consultant Review by [redacted] (b) (4) (Appendix 1), please make a concerted effort to obtain additional information on the hepatic cases that [redacted] (b) (4) said were missing important information. Please also provide from [redacted] (b) (4) an overall conclusion as to whether there is a concern for severe drug induced liver injury with alogliptin based on the available cases (unblinded and blinded) and the pattern of ALT elevation across the controlled phase 2/3 program as well as in Study 402.

Thank you!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
11/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

REVIEW EXTENSION – MAJOR AMENDMENT

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to the July 25, 2011, resubmissions of your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to our October 24, 2011, request that you conduct a comprehensive evaluation of liver-related adverse events that have occurred with alogliptin-containing products in your global clinical trial database and postmarketing setting. This information request was triggered by a postmarketing case of biochemical Hy's Law (TCI2011A04573) and numerical imbalances for alogliptin vs. comparator in serum alanine aminotransferase (ALT) elevations in your phase 2/3 program, particularly in your ongoing cardiovascular outcomes trial (Study 402).

On November 7, 2011, we received your response dated November 7, 2011, to this information request. We have determined that this 281-page response qualifies as a major amendment to your applications. Therefore, this is considered a solicited major amendment. We also note that the receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **April 25, 2012**.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at 301-796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEHREEN HAI
11/16/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request for alogliptin
Date: Thursday, October 27, 2011 4:14:07 PM
Attachments: N22271 Info Request 10-27-11.pdf

Hi Sandy,
Please find attached an information request for NDA 22271 and 22426.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Please submit the following within 3 weeks after receiving this information request.

1. Please clarify the acute pancreatitis search method used in the August 24, 2011, Analysis of Similar Events Summary submitted to alogliptin IND 69,707. In addition, clarify why the Integrated Summary of Clinical Safety in your Complete Response for alogliptin describes seven cases of acute pancreatitis (narrow scope) in controlled trials whereas the August 24, 2011, IND submission describes six cases in completed, randomized, controlled trials. Did your August 24, 2011, IND submission include a search for reports of acute pancreatitis in your completed Japanese controlled clinical trials? If not, query your phase 2 and phase 3 Japanese trials for acute pancreatitis using the same approach that you used for acute pancreatitis in your Integrated Summary of Clinical Safety for the non-Japanese pooled phase 2 and phase 3 trials. Please provide narratives for all postmarketing events of acute pancreatitis and all serious events of acute pancreatitis from your phase 2 and phase 3 Japanese trials.

2. Please provide a search of the clinical trials included in your Complete Response (including your Japanese controlled clinical trials and your uncontrolled open-label study) and postmarketing safety database for serious and nonserious events of hypersensitivity reactions. For this analysis, use the following SMQs: Anaphylactic Reaction (all narrow search terms and those patients meeting the Anaphylactic Reaction SMQ algorithm), Angioedema (show results using narrow search terms separately to results using broad search terms), and Severe Cutaneous Adverse Reactions (show results using narrow search terms separately to results using broad search terms). For the controlled clinical trials (including the Japanese trials), please tally events by the following treatment groups: alogliptin 25 mg, all alogliptin, all active comparators, and placebo. Present these results for all events (serious + non-serious) as well as separately for serious and non-serious events. Include in the top row of each table the number and percentage of patients reporting at least 1 event. Show the results from each SMQ in separate tables. Using only the narrow search terms for the three SMQs, calculate the number and percentage of patients in each treatment group who reported at least one hypersensitivity event (i.e., anaphylactic reaction and/or angioedema and/or severe cutaneous reactions). Please submit narratives for all serious events identified (or direct us to their location in your Complete Response).

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/s/

MEHREEN HAI
10/27/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request for NDA 22271
Date: Monday, October 24, 2011 3:11:25 PM
Attachments: NDA 22271 and NDA 22426 IR.pdf

Hi Sandy,
Please find attached an information request for NDA 22271 and 22426.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

We are interested in obtaining more comprehensive, updated information regarding any potential cases of drug-induced hepatotoxicity in your global clinical trial and postmarketing database for alogliptin.

Please submit your response to the following within **2 weeks** of receiving this information request.

1. Query your global clinical trial database for cases of serious liver-related adverse events (including the need for liver transplantation or death) reported in alogliptin-treated patients or in patients who are still on blinded study medication. Provide detailed narratives for any cases that were not included in your NDA submission or resubmission.
2. In your NDA resubmission, you provide a Periodic Safety Update Report for alogliptin that contains a line listing of several postmarketing liver-related adverse events, such as non-serious adverse events of “Hepatic Function Abnormal” and “Liver Disorder”. We could not locate narratives for these potential adverse events of interest. Re-query your global postmarketing database for serious and non-serious cases of liver-related adverse events. Provide detailed narratives for all identified cases.
3. Query your global clinical trial and postmarketing database for cases meeting the biochemical definition of Hy's Law (ALT > 3x ULN and total bilirubin > 2x ULN). Provide detailed narratives for those cases that were not included in your NDA submission or resubmission.
4. In your NDA resubmission, the interim results from Study 402 show a numerical imbalance not favoring alogliptin with regard to the percentage of patients with serum ALT >3x ULN, >5x ULN, and >8x ULN. Re-analyze these liver data using updated data from this trial (ensure that this analysis is adequately firewalled so as not to impact integrity of the ongoing study). For this new analysis, also include ALT >10x ULN and ALT >20x ULN.
5. Provide an updated analysis showing the number and percentage of individuals with serum ALT >3x ULN, ALT>5x ULN, ALT>10x ULN, and ALT>20x ULN based on all of your completed, controlled, phase 2 and phase 3 clinical studies to date. Include updated data from Study 402. Include data from your IND and non-IND studies (e.g., include data from the studies conducted for the Japanese regulatory authorities). Show these data for each alogliptin dose and for each comparator as well as for all alogliptin dose groups combined and all comparators combined. Include an analysis that accounts for patient-year exposure. Provide detailed narratives for those cases with serum ALT >5x ULN that were not included in your NDA submission or resubmission.

For requests 1-3 above, your searches for cases should include all available sources (e.g., spontaneous reports, post-marketing studies, completed or ongoing clinical studies) and should include patients who are on blinded study medication. Include cases involving any individual who has ever taken alogliptin for any duration, either alone or in combination with other medications (including as a fixed-dose combination). The source of the data

should be clearly indicated. Be sure to list the specific databases you queried and include the search strategy.

Include all cases (whether or not they were adjudicated) regardless of the reporters', investigators', or sponsor's attribution of causality—even if you believe there are potential confounders or plausible alternative etiologies.

Include data from all sponsored (whether or not they were designated as IND studies) and non-sponsored clinical studies.

Include updated information regarding the estimated number of patients for whom alogliptin products have been prescribed in the countries where these products are approved.

Include information on the number of patients treated with alogliptin products and comparators in your clinical trials database, including data on duration of exposure and alogliptin dose.

Please submit the requested information to both the alogliptin and alogliptin/pioglitazone FDC NDAs.

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/s/

MEHREEN HAI
10/24/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request for NDA 22271
Date: Tuesday, September 27, 2011 2:09:47 PM
Attachments: Alo IR.pdf

Hi Sandy,
Please find attached an information request for NDA 22271 and 22426.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

For Study SYR-322_301, the inclusion criteria include apolipoprotein E 3/3 or apolipoprotein E 3/4 phenotype positivity prior to baseline. Please clarify why this was a required inclusion criterion and how it impacts generalizability of results to the overall type 2 diabetes population.

For Study SYR-322_303:

1. Please complete the following table.

2. Please run the following sensitivity analyses using the same methodology that was used for the primary efficacy analysis. Each analysis should be performed using both the FAS (using LOCF after rescue) and PPS:

Analysis 1: For the glipizide arm, only include patients who reached a final glipizide dose of 10 mg daily.

Analysis 2: For the glipizide arm, only include patients who either reached a final glipizide dose of 10 mg daily or who were downtitrated from 10 mg due to hypoglycemia.

3. For glipizide, the maximum recommended total daily dose is 40 mg. Clarify why you limited the glipizide dose to only 10 mg daily, particularly if patients did not achieve adequate glycemic control on this dose.

	Number / %
I. Glipizide arm (+ alogliptin placebo)	
A. Received at least one dose of glipizide 5 mg	
1. Not uptitrated	
a. Not rescued	
i. Completed the study	
ii. Discontinued the study	
b. Was rescued (after week 12)	
2. Uptitrated to glipizide 10 mg (sometime in weeks 1-12)	
a. Not downtitrated	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
b. Downtitrated (any time from uptitration week through week 52)	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
B. Did not receive at least one dose of glipizide 5 mg (these subjects are not in the FAS?)	
II. Alogliptin arm (+ glipizide placebo)	
A. Received at least one dose of glipizide placebo 5 mg	
1. Not uptitrated	
a. Not rescued	
i. Completed the study	
ii. Discontinued the study	
b. Rescued (after week 12)	
2. Uptitrated to glipizide placebo 10 mg (sometime in weeks 1-12)	
a. Not downtitrated	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
b. Downtitrated (any time from uptitration week through week 52)	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
B. Did not receive at least one dose of glipizide placebo 5 mg (these subjects are not in the FAS?)	

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/s/

MEHREEN HAI
09/27/2011

From: Hai, Mehreen
To: Cosner, Sandra (TGRD);
Subject: Info request
Date: Tuesday, September 20, 2011 2:17:37 PM

Hi Sandy,
Got your voicemail from earlier today. I'm working from home today, but I'm happy to talk tomorrow, if you like. We don't need anything further for the pediatric plan/history, or the REMS. Regarding the inspections, that is handled by the Office of Scientific Investigations. If there are any further inspections to be done, they will get in touch with you in a timely manner, but if you still have questions, I can find out who you need to contact in OSI.

In the meantime, we have the following information request, related to the site inspections:

For studies 303 and OPI-004, were all subjects who were discontinued due to lack of efficacy actually rescued from hyperglycemia? Were there any subjects who were rescued from hyperglycemia who were not classified as having been discontinued due to lack of efficacy? Provide a list of rescued subjects by study site for these trials. Also provide a list of subjects who were discontinued due to lack of efficacy by study site for these trials.

Please provide a response at your earliest convenience.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
09/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDAs. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK
09/07/2011
J. Marchick signing for M. Parks

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: RE: NDA 22-426 REMS query
Date: Wednesday, August 31, 2011 12:55:39 PM

Hi Sandy,
Thanks for emailing me your REMS related questions. Please see our response below:

Please submit the REMS and the REMS supporting document as directed in the REMS notification letter. You can reference the previously submitted Medication Guide. There will not have been sufficient market uptake of (b) (4) to justify conducting the first assessment with the other pioglitazone products; however, if the assessment of the other pio products is adequate, then you will be able to request removal of the REMS for all of the pio products, including (b) (4)

Please let me know if this is unclear.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:scosner@tgrd.com]
Sent: Wednesday, August 31, 2011 10:37 AM
To: Hai, Mehreen
Subject: NDA 22-426 REMS query

Dear Mehreen,
In reference to the FDA letter on the Pre-approval REMS notification dated August 23, 2011, I would like to clarify a few questions. (b) (4)

(b) (4)

Takeda plans on submitting a REMS document as requested for NDA 22-426 however would like to propose that the medication guide will not be resubmitted with the REMS at this time as it had been previously submitted at the time of the resubmission on July 25, 2011. The Medication Guide will need to be updated to incorporate the most recent updates from the Actos medication guide with respect to bladder cancer, however, Takeda would propose to provide this revised Medication Guide later during the review at the time of label negotiations (b) (4)
Does the Agency agree with these proposals?

I look forward to your response. Thanks in advance.
Best regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Fax (224) 554-3646
Email: scosner@tgrd.com

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/s/

MEHREEN HAI
08/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

ACKNOWLEDGE – CLASS 2 RESPONSE INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

We acknowledge receipt on July 25, 2011, of your July 25, 2011, resubmissions of your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We consider these to be complete, class 2 responses to our action letters dated June 26, 2009 (for alogliptin) and September 2, 2009 (for alogliptin-pioglitazone fixed-dose combination). Therefore, the user fee goal date for both NDAs is **January 25, 2011**.

We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

1. Tables 8.4.2.6Ra, 8.4.2.7Ra, 8.4.2.8Ra, and 8.4.2.9Ra in the Integrated Analysis of Safety show adverse events by renal function (estimated using Cockcroft-Gault and MDRD formulas) for your controlled phase 2/3 trials. To facilitate our review, please submit revised tables presenting these data as follows:
   - Show only n (%) for each treatment group so that, for a given preferred term (PT), all treatment groups fit on one page.
   - Show results by System Organ Class and PT, but include only those PTs reported in >2% of all alogliptin-treated patients.

2. Figure 1 in the alogliptin NDA shows a graphical display of when the first primary MACE composite event occurred relative to the index acute coronary syndrome (ACS) event in cardiovascular study SYR-322_402. Please also submit the previously requested subgroup analysis evaluating the primary and secondary endpoints according to subjects with an index ACS event ≤2 months vs. >2 months prior to randomization.

3. For the alogliptin NDA, there are 36 subjects who were randomized to study SYR-322 402 and appear in the dataset *D mace* for SYR-322 402 located in Section 5.3.5.1.21.1.1, but do not appear in the dataset *D mace*, combined across studies, in Section 5.3.5.3.25.1.1. Please clarify why these subjects do not appear in the combined dataset.

4. Submit an updated pediatric development plan for both NDAs that addresses our comments from the End-of-Review meeting held on February 23, 2010. This plan should include your currently proposed ages for waiver and deferral requests together with supporting rationale. For those pediatric studies you wish to defer, provide synopses as well as a timeline for completion of the studies (this should include the date by when the final protocols will be submitted, the date by when the studies will be completed, and the data by when the complete study reports will be submitted to FDA). When determining a date for final protocol submission, you should ensure that there is sufficient time to allow FDA feedback on your draft protocols (the protocol will only be considered final after FDA agrees with the study design). We recommend that you request a full waiver for the alogliptin-pioglitazone fixed-dose combination tablet because of safety concerns with use of pioglitazone in children (e.g., risk of bladder cancer, bone effects).

5. Clarify whether there are other completed or ongoing Phase 3 studies with alogliptin or alogliptin-pioglitazone fixed-dose combination tablets that were not included in the resubmissions.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at 301-796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
08/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022426

PRE-APPROVAL REMS NOTIFICATION

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your July 25, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg and 25 mg/45 mg.

Please also refer to your approved risk evaluation and mitigation strategies (REMS) for:

- ACTOS (pioglitazone hydrochloride), originally approved on September 14, 2009 and modified on February 3, 2011 and August 4, 2011.
- ACTOPLUS MET (pioglitazone hydrochloride and metformin hydrochloride) fixed-dose combination, originally approved on September 14, 2009, and modified on October 21, 2009 and August 4, 2011.
- ACTOPLUS MET XR (pioglitazone hydrochloride and metformin hydrochloride extended-release) fixed-dose combination, originally approved on May 12, 2009 and modified on December 22, 2010 and August 4, 2011.
- DUETACT (pioglitazone hydrochloride and glimepiride) fixed-dose combination, originally approved on September 9, 2009 and modified on August 4, 2011.

These REMS consist of a Medication Guide and a timetable for submission of assessments of the REMS.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for (b) (4) (alogliptin/pioglitazone fixed-dose combination) to ensure the benefits of the drug outweigh the risks of congestive heart failure in patients being treated with pioglitazone.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide, as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that (b) (4) (alogliptin/pioglitazone fixed-dose combination) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of (b) (4) (alogliptin/pioglitazone fixed-dose combination). FDA has determined that (b) (4) (alogliptin/pioglitazone fixed-dose combination) has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use (b) (4) (alogliptin/pioglitazone fixed-dose combination).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed (b) (4) (alogliptin/pioglitazone fixed-dose combination).

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to (b) (4) (alogliptin/pioglitazone fixed-dose combination) (see Appendix A). Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

For administrative purposes, designate the proposed REMS submission as "**PROPOSED REMS for NDA 022426**" and all subsequent submissions related to the proposed REMS as "**PROPOSED REMS-AMENDMENT for NDA 022426**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at 301-796-5073.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

ENCLOSURES:
REMS Appendices A and B

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

To inform patients about the serious risks associated with the use of [drug name].

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments [include only for NDA and BLA, not ANDA]

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B:

REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Medication Guide
    b. Describe in detail how you will comply with 21 CFR 208.24
    c. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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/s/

AMY G EGAN
08/23/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Response to NDA 22426 submission dated July 27, 2011
Date: Tuesday, August 09, 2011 10:35:28 AM

Hi Sandy,
Please see our response below to your July 27, 2011 submission to the alogliptin-pioglitazone NDA 22426, regarding the drug product dissolution method. Your comments and questions are in plain font, and our response is in bold font.

==========

1. Takeda has demonstrated that the pioglitazone specification of Q= (b) (4) in 30 minutes is fully justified and capable of discriminating important product differences/changes. Takeda requests FDA's concurrence.

FDA Response: We do not agree with this proposal because the data presented show that a Q = (b) (4) at 15 minute can be met for pioglitazone.

2. If the Agency does not concur with point #1 above, Takeda will commit 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 in the first Annual Report.

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.

FDA Response: Your second proposal is acceptable.

==========

Please let me know if you have any questions.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/10/2011

Marchick, Julie

From: Marchick, Julie
Sent: Thursday, July 28, 2011 10:53 AM
To: 'allison.villinski@tgrd.com'; 'scosner@tgrd.com'
Cc: Hai, Mehreen
Subject: NDA 22271 and NDA 22426 Alogliptin and Alogliptin/Pioglitazone - Information Request

Good Morning Allison and Sandy,

We have the following requests. Please let us know when you anticipate you will be able to submit this information.

1. In the preliminary minutes for our June 20, 2011 meeting, we provided a list of the information needed to determine which clinical site inspections will be conducted for EXAMINE. We could not find this information in the NDA submission. Please clarify where this information is located in the NDA submission. If it is not in the NDA, please submit the information. At a minimum, we need the following information for Study 402 as soon as possible to start the inspection process:
(A) a listing by site of the number of patients screened, enrolled and discontinued,
(B) a listing of the contact information for each site. You may model your response on that found under Module 5.3.5.1.7 for Study SYR-322-303 in your Alogliptin submission.

2. Please submit an updated pediatric development plan with timelines for NDAs 22-271 and 22-426. This plan should include your currently proposed ages for waiver and deferral requests together with supporting rationale. For those pediatric studies you wish to defer, provide synopses as well as a timeline for completion of the studies (this should include the date when the final protocols will be submitted, the date when the studies will be completed, and the data when the complete study reports will be submitted to FDA). When determining a date for final protocol submission, you should ensure that there is sufficient time to allow FDA feedback on your draft protocols (the protocol will only be considered final after FDA agrees with the study design).

Thanks,
Julie

Julie Marchick
Acting Chief, Regulatory Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

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/s/

JULIE C MARCHICK
07/28/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Response to your questions
Date: Wednesday, July 20, 2011 4:51:51 PM

Hi Sandy,
In response to the two questions you asked me on Monday:

1) Regarding the information we need for the clinical site inspections, please provide only the following info for each of the other Phase 3 trials that you plan to include in the NDA resubmission, in a tabular format by site.

a. Number of subjects screened for each site by site
b. Number of subjects randomized for each site by site
c. Number of subjects treated who prematurely discontinued for each site by site

Please try to include this information in the NDA resubmission. Also, in response to your voicemail this morning, please also include this information for the studies that have been inspected previously, since that is likely to have been a while ago. You can mention in your submission that they were previously inspected.

2) Regarding the response to our Biopharm comment, you may respond to our comment after resubmission of the NDA. However, it will be better if you can send us a concurrence as soon as possible about whether or not you agree to our request so that you can update your ongoing stability program based on our proposed specification. Also, if you have samples taken as per our recommendation, you need to submit them as soon as possible. But none of this should hold up your NDA resubmission.

Please let me know if this is not clear.
I'm working from home today, so please email me if you need further clarification.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073

Fax: 301-796-9712

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/s/

MEHREEN HAI
07/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to the teleconference between representatives of your firm and the FDA on June 20, 2011. The purpose of the meeting was to discuss the upcoming re-submissions of the referenced NDAs in response to our Complete Response letters dated June 26, 2009 (alogliptin) and September 2, 2009 (alogliptin and pioglitazone fixed-dose combination).

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance
Meeting Date and Time:	Monday, June 20, 2011, 1:00 – 2:00 PM (Eastern)
Meeting Location:	Teleconference
Application Number:	NDA 022271 and NDA 022426
Product Name:	Alogliptin tablets Alogliptin and pioglitazone fixed-dose combination tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Hylton Joffe, MD, MMSc
Meeting Recorder:	Mehreen Hai, PhD

FDA ATTENDEES

Mary Parks, MD	Director, Division of Metabolism and Endocrinology Products (DMEP)
Hylton Joffe, MD, MMSc	Diabetes Clinical Team Leader, DMEP
Ilan Irony, MD	Diabetes Clinical Team Leader, DMEP
Valerie Pratt, MD	Clinical Reviewer, DMEP
Eugenio Andraca-Carrera, PhD	Statistics Reviewer, Division of Biometrics VII
Todd Sahlroot, PhD	Deputy Director, Division of Biometrics II
Janice Derr, PhD	Statistics Reviewer, Division of Biometrics II
Julie Marchick, MPH	Acting Chief, Project Management Staff, DMEP
Mehreen Hai, PhD	Regulatory Project Manager, DMEP
Susan Leibenhaut, MD	Medical Officer, Division of Scientific Investigations

SPONSOR ATTENDEES

Sandra Cosner, RPh	Associate Director, Regulatory Affairs
Penny Fleck, MT	Director, Clinical Science
Thomas Harris, RPh	Vice President, Regulatory Affairs
Mick Roebel, PhD	Senior Director, Regulatory Affairs
Nancy Siepman, PhD	Vice President, Analytical Science
Thomas Strack, MD	Vice President, Clinical Science
Allison Villinski, MS	Director, Regulatory Affairs
Craig Wilson, PhD	Principal Statistician, Biostatistics

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for the alogliptin-pioglitazone fixed-dose combination tablet on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist approved by FDA on July 15, 1999, under NDA 021073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009, for NDA 022426.

Takeda intends to resubmit these two NDAs in July 2011. The purpose of this meeting was to discuss the upcoming resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426, and to address particular aspects of the ongoing cardiovascular outcomes trial (EXAMINE) for alogliptin.

2. DISCUSSION

Your questions are repeated below in plain font. Our preliminary responses sent to you on June 17, 2011, follow in bold font. A summary of the meeting discussion is shown in italic bold font. Post-meeting comments are shown in underlined plain font.

Question 1:

As has been discussed previously with the Division, Takeda has established appropriate firewalls to ensure that the ongoing conduct of EXAMINE is being performed by individuals who have not been made aware of the results from the interim analysis. Based on the outcome of the Agency's review, EXAMINE could be ongoing at the time of the Agency's approval of alogliptin.

Has the Agency considered how the integrity of the double blind study will be maintained after approval in light of the Freedom of Information Act (FOI) (e.g. redaction of the EXAMINE interim analysis results in reviews posted on the Drugs@FDA website)?

FDA Preliminary Response: Yes. Interim results from ongoing cardiovascular outcomes trials for anti-diabetic medications will be redacted from FDA's clinical and statistical reviews prior to posting of these reviews on the FDA website. In addition, these interim results will not be included in the approved package insert.

Meeting Discussion: Takeda clarified that all of its personnel present at this teleconference call have already been unblinded to the interim results of EXAMINE.

FDA confirmed that we will redact portions of our reviews that discuss interim results from EXAMINE before the reviews are posted publicly. As an additional safeguard, FDA recommended that Takeda clearly identify in their resubmission all data that are derived from interim analyses of EXAMINE that should not be disclosed in public FDA reviews. Takeda offered to read FDA reviews to help identify any data that should be kept confidential but FDA

explained that our policy is not to share our reviews with anyone outside FDA prior to the public posting.

Question 2:

During the Post-Action Feedback meeting with the Agency on January 12, 2010 and the End-of-Review meeting held on February 23, 2010, Takeda stressed its high level of commitment to submitting complete and high quality re-submissions for the alogliptin and alogliptin/pioglitazone FDC. In addition, Takeda emphasized the need for timely communications, transparency and review efficiencies within the Agency following the re-submissions. To that end, Takeda would like the Agency to re-confirm the following:

a) The user fee goal date for a re-submission is 6 months from receipt of the amendment to the NDA. If the alogliptin and alogliptin/pioglitazone FDC re-submissions are provided to the Agency at the same time, they will be on the same review clock and have the same user fee goal date.

FDA Preliminary Response: Yes, that is correct.

Meeting Discussion: There was no discussion of this response.

b) Labeling discussions will begin at least 4 weeks prior to the scheduled action dates should the data from the application support approval.

FDA Preliminary Response: Yes, that is correct.

Meeting Discussion: There was no discussion of this response.

c) The proposed tradenames for alogliptin and alogliptin/pioglitazone FDC (Nesina and (b) (4) respectively) will be reviewed within 90 days of the NDA re-submissions.

FDA Preliminary Response: Yes, that is correct. Please refer to the Guidance for Industry entitled *Contents of a Complete Submission for the Evaluation of Proprietary Names* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf).

Meeting Discussion: Takeda raised additional questions about the tradename review process, such as concurrent submission of other tradenames in case the currently proposed tradenames are found unacceptable. FDA recommended that Takeda follow the guidance mentioned above and that, if there are any remaining questions, that those questions be submitted for review by the Division of Medication Error Prevention and Analysis (DMEPA).

d) In general, the re-submission review timelines will be communicated to the Sponsor so that Takeda can promptly provide responses to the Agency's requests, ensuring efficiency of the overall review process.

FDA Preliminary Response: We will establish internal timelines to ensure timely review of your re-submissions within the 6-month review clock. Early in the review process, we will inform you of when we expect to communicate proposed labeling and, if necessary, any requests for postmarketing commitments or postmarketing requirements. If we have information requests during our review we will send these to you as soon as they are identified.

Meeting Discussion: There was no discussion of this response.

e) Does the Agency anticipate conducting clinical site inspection(s) based on the additional studies included in the re-submission? If so, what is the timing with respect to the review clock for the conduct and completion of the site inspection(s)?

FDA Preliminary Response: A determination of whether or not clinical site inspections need to be conducted will be made at the time of NDA re-submission. Because of the short timeline, in order for us to efficiently prepare for inspections, we request that the information in the attached documents be submitted at the time of the submission of the application.

Meeting Discussion: Takeda clarified that it will provide this information.

Post-Meeting Comment: Given your intent to submit other Phase 3 trial reports with EXAMINE (e.g. elderly study report and trials with pioglitazone), please include the above requested information for those trials as well.

f) Although no new Chemistry, Manufacturing and Controls (CMC) information will be included in the re-submissions, does the Agency anticipate conducting Prior Approval Inspections (PAIs) of the manufacturing facilities?

FDA Preliminary Response: Yes, we may decide to conduct a PAI. Form FDA 356h of the resubmissions should include all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and a statement that they are immediately ready for GMP-inspection.

Meeting Discussion: There was no discussion of this response.

g) Can the Agency confirm that if the issues cited in the Complete Response Letter have been adequately addressed and no further issues are identified during the review, an Advisory Committee meeting would not be necessary?

FDA Preliminary Response: An advisory committee (AC) meeting will likely not be needed if we determine that you definitively address the deficiencies in the Complete Response letter and we do not identify any unexpected efficacy or safety findings during our review. A final determination of whether or not an AC meeting will be required will be made after NDA re-submission.

Meeting Discussion: There was no discussion of this response.

Question 3:

Takeda would like to propose language to be included in the prescribing information (e.g. under Adverse Reactions) with the available cardiovascular safety data on alogliptin. (b) (4)

While Takeda recognizes that the Agency cannot comment on specific labeling language at this time, will the Agency consider Takeda's proposal to provide physicians cardiovascular safety information based on a meta-analyses that includes integration of the EXAMINE interim data?

FDA Preliminary Response: No. FDA is not permitting cardiovascular outcomes data that meet the 1.8 cutpoint in approved labeling, regardless of whether these data are derived from completed or ongoing trials. Approval of a new treatment for type 2 diabetes implies that the 1.8 cutpoint has been met because our Guidance states that this cutpoint must be met to support approval. Please also see our response to Question 1.

Please also respond to the following questions:

1. **Question 3 states** (b) (4)
   Please clarify to which (b) (4) **you are referring.**
2. **What is the status of the EXAMINE study with respect to the pre-specified group sequential procedure corresponding to the 1.8 hazard ratio non-inferiority margin? The procedure specifies interim analyses at 80, 100, and 125 adjudicated primary MACE events and a final analysis at 150 events. We would like to know the total number of adjudicated primary events in the MACE composite in EXAMINE that were analyzed and used as the basis of the decision to re-submit the NDA. We would also like to confirm (yes or no) that the test statistic for this analysis satisfied the group sequential boundary. However, until the time the NDA is re-submitted, we would like to remain blinded to the number of events in each treatment arm and to the value of the test statistic.**
3. **What is the anticipated number of patients with at least one year of exposure to study drug in the EXAMINE trial at the time of NDA resubmission? What is the anticipated mean exposure for the trial?**
4. **Clarify what else you are planning to include in the NDA resubmission besides the interim results from EXAMINE.**

Meeting Discussion: ***Takeda asked if selected information from the interim results for EXAMINE (e.g., patient demographics) could be included in labeling. FDA stated that Takeda should include the proposed labeling with the resubmission, together with rationale for data they would like to include from EXAMINE. A final decision will be made after FDA has reviewed the resubmission.***

Follow up discussion of Sub-Question 1: Takeda stated that they will submit a MACE analysis (death, myocardial infarction, and stroke) based on the interim data from the EXAMINE trial alone as well as a meta-analysis of the interim results from EXAMINE together with the completed Phase 2/3 trials. FDA stated that this is acceptable but that, as discussed on April 27, 2009, the EXAMINE trial must be able to stand alone for addressing cardiovascular (CV) safety for alogliptin.

Follow up discussion of Sub-Question 2: Takeda said it achieved the 1.8 non-inferiority margin with (b)(4) events of death, myocardial infarction, and stroke. Takeda used an alpha of 0.002 consistent with the pre-specified group sequential test at the first interim analysis scheduled for 80 events. FDA thanked Takeda for providing this information.

Follow up discussion of Sub-Question 3: Takeda stated that the resubmission will contain data on 526 patients (400 patients combined in trials 1 and 2 below; 100 patients in EXAMINE) exposed to alogliptin for >1 year in the following three new trials:

1. ***Alogliptin versus pioglitazone trial***
2. ***Alogliptin versus sulfonylurea trial in the elderly***
3. ***EXAMINE trial: Approximately 100 patients per treatment arm with >1 year exposure to study medication with a mean exposure of 5-6 months. This trial is still enrolling.***

Follow up discussion of Sub-Question 4: Takeda plans to submit the following new trials: EXAMINE, two Phase 3 studies, two Phase 1 studies, Japanese (safety) studies, and non-clinical data, as per discussions at the February 23, 2010, End-of-Review meeting. No Chemistry/Manufacturing/Controls (CMC) information will be submitted.

FDA asked Takeda to clarify its pooling strategy for the new Phase 3 trials. Takeda stated that the safety analysis will be similar to that discussed at the February 2010 End-of-Review meeting. The safety data will be pooled with and without EXAMINE. Old versus new data will be highlighted. Changes in the incidence of adverse events and serious adverse events between the initial submission and resubmission will be discussed. FDA asked Takeda to send in a synopsis of how the Phase 2/3 data will be presented in the planned NDA resubmission. Takeda agreed and clarified that the goal NDA resubmission date for both NDAs is July 25, 2011.

Post-Meeting Comment: Takeda provided the table of contents for the proposed resubmissions by email on July 8, 2011, but this document does not explicitly state how the data will be presented. Takeda should specifically clarify if there are any deviations from agreements reached at the End-of-Review meeting regarding content and data presentation for the resubmissions.

Question 4:

As per Takeda's agreement with the Agency, Takeda is planning on continuing the EXAMINE trial until the protocol planned final analysis. However, the Data Monitoring Committee (DMC) has recently requested guidance on how to proceed with reviewing the cardiovascular safety data from the ongoing EXAMINE trial should the MACE hazard be [redacted] (b) (4) Takeda would like to discuss guidance that can be given to the DMC to ensure that the study is not stopped until the study has [redacted] (b) (4) Following the NDA re-submissions, Takeda plans to submit a meeting request to discuss this topic further.

Does the Agency agree with Takeda's proposal?

FDA Preliminary Response: Based upon information submitted in your briefing jacket, it is unclear how a [redacted] (b) (4) would be incorporated into your protocol. Based on the pre-specified statistical plan for assessing the 1.3 margin, it appears that you will not [redacted] (b) (4) More detailed information on your proposed changes to the study design and stopping rules is needed in order to evaluate your proposal. With that being said, the following are some points to consider.

[redacted] (b) (4) **Please, therefore, submit your meeting request to discuss this topic prior to NDA resubmission and our review of the data.**

[redacted] (b) (4) **Adequate statistical and operational justification should be provided for any proposed changes, including details on the alpha-spending function and power. If previously submitted simulations are no longer representative of the modified trial, a new set of simulations may be required. All proposed changes should also be discussed and approved by the DMC to ensure they are in the best interest of the patients. If at some point the DMC recommends prematurely stopping EXAMINE, we recommend that you notify FDA before stopping the trial.**

Meeting Discussion: ***Takeda agreed to submit a Type B meeting request to discuss this issue prior to NDA resubmission and asked for an expedited review and meeting date. FDA responded that we will do our best to accommodate the requested timeline but cannot guarantee that we could do so. Takeda replied that it will propose an analysis plan for*** [redacted] (b) (4)

FDA followed up on Takeda's initial statement that all of its teleconference participants were unblinded to the study results. FDA asked who from Takeda will be writing the revised plan (b)(4) Takeda replied that they had planned to have the unblinded team do so. FDA responded that our goal is to be as objective as possible when reviewing the statistical analysis plan by remaining blinded to study results and that Takeda should do the same. Takeda agreed to do so.

Post-Meeting Comment:

On June 22, 2011, FDA sent the following email to Takeda:

"During the June 20th, 2011 teleconference with the Agency to discuss NDA 022271 and NDA 022426, Takeda discussed the first interim analysis of the EXAMINE trial. The first interim analysis was conducted according to the pre-specified plan after (b)(4) MACE events have been observed in EXAMINE. According to Takeda, the results of this interim analysis achieved the 1.8 non-inferiority margin for the relative risk of MACE. The EXAMINE protocol states that the next interim analysis will test for a non-inferiority margin of 1.3 after 550 events have been observed. Takeda discussed their wish to deviate from the original EXAMINE protocol to allow for an interim analysis for non-inferiority, (b)(4). The timing proposed for this additional interim analysis, in terms of number of events, was not discussed during the teleconference.

In general, data driven changes in the timing of interim analyses present a challenge and are to be avoided. It is often difficult or impossible to evaluate the statistical properties of tests conducted at these data driven interim looks. Both Takeda and the Agency should try to be as objective as possible when writing and reviewing proposed changes to a statistical analysis plan. In the case of the EXAMINE trial, it is known that the noninferiority margin of 1.8 was met at (b)(4) events. This information sets a bound for the observed relative risk of MACE at (b)(4) events. Therefore all additional, not previously planned, interim analyses in EXAMINE are unblinded to the available data.

During the teleconference, the Agency agreed to further discuss Takeda's proposal. We recommend that you consider that any additional interim analyses in the EXAMINE trial should maintain the Type I error for noninferiority, and should minimize the potential bias resulting from knowing the results of the first interim analysis. The following two approaches meet these criteria; you may propose other approaches as long as they maintain Type I error and minimize bias:

1) Use of a Peto-type stopping rule. This approach spends a very low alpha at each interim look and allows for an unspecified number of interim looks.
2) Consider using the first (b)(4) events in the EXAMINE trial as a pilot study from which to estimate the statistical characteristics of the remainder of the study. The results of the additional proposed interim analysis at n events would be based only on the last n-(b)(4) events.

We also would like to remind Takeda of our interest, as part of the complete response submission, in a subgroup analysis that evaluates the primary and secondary endpoints of the

EXAMINE study, according to subjects with an ACS event ≤ 2 months versus subjects with an ACS event > 2 months prior to randomization."

Takeda responded on June 28, 2011 by email stating:

"Thank you again for the informative teleconference that was held with the Division on June 20th as well as the e-mail communication regarding the ongoing cardiovascular outcomes trial (Study 402, EXAMINE) sent on June 22nd. Based on the feedback that Takeda has received from the Agency and internal discussions, Takeda has decided not to make any revisions to the protocol or Statistical Analysis Plan (SAP) for EXAMINE.

However, as noted in the June 20th teleconference, Takeda is looking for clarification from the Agency on the requirements needed to [redacted] (b) (4)

Although we are no longer planning to modify the statistical plan, we remain concerned that it is the DMC's desire to request their own analysis of the primary endpoint prior to the next interim look at 550 events and recommend the study stop early on the basis of preserving subject safety for those randomized [redacted] (b) (4) Takeda proposes that the DMC informs Takeda of its intentions to conduct an interim analysis prior to 550 MACE. Takeda would in turn contact the Agency and suggest that, without Takeda being involved, direct discussions between the DMC and the Division occur regarding the appropriateness of such an unplanned analysis and potentially stopping the study prior to reaching the protocol defined first interim analysis and its potential impact on [redacted] (b) (4) Does the Agency agree with this approach? Takeda will gain DMC's agreement with this proposal after it is agreed by the Agency.

In summary, Takeda is no longer planning on submitting a proposal to the Agency for consideration, but would appreciate a response to the questions posed above to ensure that there are no outstanding issues related to the ongoing conduct of EXAMINE prior to the filing of the NDA re-submissions."

FDA response to Takeda's June 28, 2011, email:

We understand you to say that you do not plan to conduct an analysis with respect to the 1.3 margin before the next pre-specified interim analysis at 550 events as was suggested during the teleconference. Therefore the first planned interim analysis for testing the 1.3 non-inferiority margin will occur at 550 events.

[redacted] (b) (4)

(b) (4)

We agree to direct discussion with the DMC without Takeda involvement regarding the appropriateness of any unplanned analyses that may potentially stop the study prior to reaching the protocol defined first interim analysis at 550 events. (b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor will submit an updated summary of the data contained in the upcoming NDA resubmissions	Sponsor	Submitted by email on July 8, 2011.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

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/s/

MEHREEN HAI
07/15/2011

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Thursday, July 14, 2011 11:54 AM
To: 'scosner@tgrd.com'
Subject: NDA 22-426 Response to 5/31/2011 submission

Dear Ms. Cosner,

Please refer to your NDA submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Alogliptin/Pioglitazone Fixed Dose Combination (FDC) Tablets. We also refer to your amendment dated May 31, 2011.

We have the following comments and recommendation:

Please adopt a Q= (b) (4) at 15 minutes for pioglitazone using the proposed dissolution method with PEAK vessels at 50rpm. You are advised to contact the Agency with supportive data at 15 minutes for pioglitazone if problems arise in adhering to the above specifications.

Please let me know if you have any questions or concerns.

Khushboo Sharma
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
07/14/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: RE: NDA 22-271 and NDA 22-426 Meeting Request Submission
Date: Thursday, May 26, 2011 2:41:31 PM

Hi Sandy,
We are confirmed for the tcon on Monday, June 20, 2011, from 1:00 - 2:00 PM (Eastern).
The attendees will be Dr. Mary Parks, Dr. Ilan Irony, Dr. Hylton Joffe, Dr. Valerie Pratt, Dr. Eugenio Andraca-Carrera and myself. If there are any additions/changes, I will let you know closer to the date of the tcon.

Can you please provide a call-in number?
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:scosner@tgrd.com]
Sent: Thursday, May 26, 2011 12:30 PM
To: Hai, Mehreen
Subject: RE: NDA 22-271 and NDA 22-426 Meeting Request Submission

Dear Mehreen,
Thank you so much for responding so quickly and accommodating our earlier request. June 20th from 1- 2:00 PM will work for our Takeda team. Can you please confirm if this is Eastern time? Also, will you be providing a call in number and also confirming the attendees from the FDA staff?
Thank you again.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Fax (224) 554-7870
Email: scosner@tgrd.com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Thursday, May 26, 2011 10:11 AM
To: Cosner, Sandra (TGRD)
Subject: RE: NDA 22-271 and NDA 22-426 Meeting Request Submission

Hi Sandy,
We did our best to schedule your tcon as soon as possible, but I'm afraid the earliest we were able to schedule for is June 20, 1:00 - 2:00 PM. Does this work for you?

Please let me know.
Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:scosner@tgrd.com]
Sent: Wednesday, May 25, 2011 4:15 PM
To: Hai, Mehreen
Subject: NDA 22-271 and NDA 22-426 Meeting Request Submission

Dear Mehreen,
We are submitting a meeting request today for the alogliptin and the alogliptin/pioglitazone FDC NDAs (22-271 and 22-462, respectively). I have included the submission as an attachment for your reference. This is following recent emails in April and May between Takeda and Dr. Parks of our intent to schedule a teleconference with the Agency within the next couple of weeks prior to our resubmissions to the Complete Response letters. We look forward to discussing these few issues with the Agency soon.
Please let me know if you have any questions.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Fax (224) 554-7870
Email: scosner@tgrd.com

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/s/

MEHREEN HAI
05/26/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
cc: Le, Trang (TGRD);
Subject: RE: NDA 22-426 Request for Advice- CMC
Date: Wednesday, April 20, 2011 3:35:04 PM

Hi Sandra,
Please see our response below (in red) to the request for advice regarding NDA 022426 (alogliptin-pioglitazone FDC) that you emailed me and submitted officially to the NDA on April 19, 2011:

FDA Response: Yes, we agree with your proposal. Please include the full development and validation report with associated data at the time of your submission.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:scosner@tgrd.com]
Sent: Monday, April 11, 2011 9:40 AM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD); Le, Trang (TGRD)
Subject: NDA 22-426 Request for Advice- CMC

Dear Mehreen,
Please refer to the New Drug Application 22-426 for SYR-322-4833 fixed-dose combination (FDC) tablets submitted by Takeda Global Research & Development Center, Inc. (TGRD) under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

The purpose of this email is to:

1) Provide an update to the Agency on the evaluation of the requested paddle speed change in the drug product dissolution method, as committed by TGRD, and
2) Propose an alternate dissolution method, based upon the evaluation in (1) above, and the timing for submission of this new method.

Regarding TGRD's commitment to evaluate the paddle speed change in the drug product dissolution method, please refer to the CMC information request letter dated 09 June 2009, a follow-up FDA e-mail request received on 17 June 2009, and TGRD's response letter for a Phase IV agreement dated 18 June 2009 (NDA 22-426; Sequence No. 0016). In summary, TGRD's commitment to evaluate a change to the dissolution method for the SYR•322•4833 FDC tablets included the following:

- TGRD will commit to further evaluating a change in the analytical procedure for dissolution of SYR-322-4833 tablets (changing paddle speed (b) (4) to 50 rpm).
- Dissolution profile data will be gathered 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.
- If the additional 50 rpm data confirms that the method is reliable and compatible with the agreed specifications, the method change will be implemented within 1 year after product approval and reported in the first NDA Annual Report.
- Until implementation of this change, product release and stability testing will continue with the

originally proposed (b) (4) method.

Updated summary of dissolution method development work and stability studies:

1. Data from ongoing stability studies and additional development work on the dissolution method indicate that changing only the paddle speed of the current method (b) (4) 50 rpm yields unacceptable results (b) (4)
2. Stability results of recent product batches have shown (b) (4)
3. The change in paddle speed (b) (4) to 50 rpm, as requested by the Agency, (b) (4)
4. Consequently, a new dissolution method has been developed using the 50 rpm paddle speed with PEAK vessels (b) (4) Other test method parameters and the Q specifications remain unchanged.

Proposed new dissolution method and timing of submission:

Based upon the additional development work and results described above, TGRD would like to submit the new 50 rpm/PEAK vessel dissolution method as the commercial dissolution method for the SYR-322-4833 FDC. This change in dissolution method would be implemented at the time of approval of the NDA. As a reminder, TGRD was not planning to include any Module 3 updates for the resubmission of this FDC product, as previously discussed with the Agency at the Type B meeting held on February 23, 2010. However, due to the recent developments summarized above, and to allow sufficient review time of the proposed method change, TGRD would like to provide the proposed dissolution method and associated justification for the Agency's review prior to the NDA resubmission. We plan to update Module 3 Sections 3.2.P.2.2.1 (Development of Dissolution Test Conditions) and 3.2.P.5.2 (Analytical Procedure - Dissolution). Final reports would be available for submission to the Agency by the end of May 2011.

Does the Agency agree with this proposal for Takeda to submit, for the Agency's review, data to support the new 50 rpm/PEAK vessel dissolution method for SYR-322-4833 FDC prior to the NDA resubmission? This change in dissolution method would be implemented at the time of approval of the NDA.

We would be glad to request a meeting to further discuss this dissolution method change proposal. I have copied Trang Le, the Regulatory Affairs Strategy – CMC Manager, responsible for this product. Please do not hesitate to contact us if you have any additional questions.

Sincerely,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Fax (224) 554-7870
Email: scosner@tgrd.com

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/s/

MEHREEN HAI
04/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

GENERAL ADVICE

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin and pioglitazone fixed-dose combination tablets.

We also refer to the minutes that we issued on March 16, 2010, for the End-of-Review meeting that was held on February 23, 2010 between representatives of your firm and the FDA. The purpose of the meeting was to discuss the planned resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426. Finally, we refer to your submission dated April 13, 2010, containing comments and requested revisions to the official meeting minutes.

Please find below our responses to your requested revisions. The text from the original meeting minutes is shown in italic font, your comments are underlined, and our current responses are shown in bold font. Please note that our responses were previously communicated to you by email on May 5, 2010.

Question 11: Does the Agency agree with Takeda's definitions for the special interest adverse events?

FDA Preliminary Response: No, we do not agree. Please also do the following:

- *Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.*
- *In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.*
- *For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).*

Meeting Discussion: The sponsor agreed to broaden its definition of PCDR to include skin ulcer-related events (bullet #1) and to submit the new list of preferred terms for review.

Regarding bullet #2, the sponsor clarified that serum amylase and pancreatitis data are only routinely collected in study 402. These data will be submitted. Laboratory and imaging data in confirmed cases of pancreatitis (including those cases occurring in the other studies) will also be submitted.

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor agreed to analyze all available data. The Division agreed with this approach.

TGRD Comment: Regarding bullet #3, TGRD explained that majority of the infections that will occur with alogliptin will be non-serious and therefore, organism types are unlikely to be determined or available. For infections that are serious adverse events, TGRD noted that organism type will not be captured in the clinical database, but if assessed, will be reported in the patient narrative. TGRD recalls during the meeting the Division accepting the reasons that analysis of these data are not possible. Therefore, TGRD would like to suggest the following revision to the third paragraph to capture the meeting discussions more accurately:

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor indicated that for infections that are serious adverse events, if organism type is assessed, it will be reported in the patient narrative. However, no analysis of such data will be performed since organism type will not be captured in the clinical database. The Division agreed with this approach.

FDA Response: We find your revision acceptable.

Question 18: Does the Agency agree with Takeda's proposal [redacted] (b) (4)

FDA Pre-Meeting Response: No, we do not agree. The proposal [redacted] (b) (4) *will be a review issue.*

[redacted] (b) (4)

(b) (4)

[redacted]

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Copy of letter with meeting minutes dated March 16, 2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets and for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on February 23, 2010. The purpose of the meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Review Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Review

Meeting Date and Time: February 23, 2010, 1:30 PM – 2:30 PM (Eastern)
Meeting Location: White Oak Campus, Building 22, Silver Spring, MD

Application Number: NDA 022271 and NDA 022426
Product Name: Nesina (alogliptin) Tablets and
(b) (4) (alogliptin/pioglitazone FDC) Tablets
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Takeda Global Research & Development Center, Inc.

Meeting Chair: Valerie Pratt, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Curtis Rosebraugh, M.D., M.P.H.	Director, Office of Drug Evaluation II (ODE II)
Mary Parks, M.D.	Director, Division of Metabolic and Endocrinology Products (DMEP)
Hylton Joffe, M.D., M.M.Sc.	Diabetes Team Leader, DMEP
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology II
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Statistics Reviewer, Division of Biometrics II
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Linda Galgay, R.N.	Regulatory Project Manager, DMEP
Arlet Nedeltcheva-Peneva, M.D.	Clinical Reviewer, DMEP

SPONSOR ATTENDEES

Thomas Strack, M.D.	Vice President, Clinical Science
Penny Fleck, M.T.	Director, Clinical Science
Neila Smith, M.D.	Senior Medical Director, Pharmacovigilance
Michie Hisada, M.D.	Medical Director, Pharmacovigilance
Craig Wilson, Ph.D.	Principal Statistician, Biostatistics
Vipin Arora, Ph.D.	Associate Director, Biostatistics
Dan Bollinger, R.Ph.	Principal Scientist, Pharmaceutical Science

Rebecca Adams	Assistant Project Director, Project Management
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Sangeeta Gupte, Ph.D.	Manager, Regulatory Affairs
Christie Idemoto, M.S.	Associate Director, Regulatory Affairs
Yukari Nishikata	Senior Director, Takeda Japan Liaison
Riccardo Camisasca, M.D.	Medical Director, Clinical Science (Europe)

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 21-073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009 for NDA 022426.

The purpose of this meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

2. DISCUSSION

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the Sponsor on February 20, 2010, follow in bold. A summary of the meeting discussion is shown in italicized bold font.

Question 1: Does the Agency agree with the proposed structure and contents of both NDA resubmissions?

FDA Preliminary Response: Yes, but with exceptions noted in the comments below.

Meeting Discussion: There was no discussion.

Question 2: Does the Agency agree with Takeda's plan to summarize all integrated safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Please clarify. Does the question only pertain to the location of the integrated safety data or are you proposing to present these data differently?

Clarify why you are not including Study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the alogliptin/pioglitazone fixed-dose combination NDA.

Meeting Discussion: ***The sponsor clarified that the question pertains only the location of the integrated safety data.***

Study 009 will not be included in the integrated safety analysis for the fixed-dose combination (FDC) product because these subjects were on a thiazolidinedione (TZD) for months to years before starting alogliptin, whereas the subjects in the proposed integrated analysis will be randomized to simultaneously start alogliptin + pioglitazone. Study 009 was not included in the integrated analyses of the original NDAs for the same reason. The Division concurred that it is acceptable to not include Study 009 in the integrated analysis for the FDC product in the Complete Response.

Question 3: For the Safety Updates, Takeda plans to summarize relevant safety data (adverse events, SAEs, and adverse events leading to discontinuation) from the individual Japanese studies within Module 2.7.4 and provide the final clinical study reports for these non-IND studies in Module 5. Does the Agency find this approach acceptable?

FDA Preliminary Response: Yes, this is acceptable. Please cite the table numbers in the original study reports and provide hyperlinks where possible.

Meeting Discussion: ***There was no discussion.***

Question 4: Does the Agency agree that the proposed integrated analyses of the phase 2 and 3 controlled studies as described in the SAPs, and the table shells are adequately designed to address the Agency's requests in Complete Response letters for the both alogliptin alogliptin/pioglitazone safety updates?

FDA Preliminary Response: Yes, but with the following caveats:

- **Please also summarize duration of exposure to study medication according to baseline renal function (mild, moderate, and, severe renal impairment as calculated by both the Cockcroft-Gault and MDRD formulae).**
- **You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline) because such an increase in serum creatinine even within the reference range may reflect an important decline in renal function. If you wish to also analyze renal data with the revised definition, you may do so.**
- **Please clarify if adverse events will be summarized in the pooled study population and by individual study (including recently completed studies).**

Meeting Discussion: ***The sponsor agreed to bullets #1-2. The sponsor stated that adverse events will be summarized by pooled study population and in the newly completed individual studies. Hyperlinks will be provided to adverse events in the study reports submitted with the original NDAs. The Division stated that this approach is acceptable.***

Question 5: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, these are acceptable.

Meeting Discussion: ***There was no discussion.***

Question 6: Does the Agency agree that the proposed primary and secondary MACE analyses as described in the SAP and the table shells for Study 402 are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify the minimum duration of treatment exposure for all patients enrolled in Study 402. If you intend to prematurely terminate Study 402 (e.g., if you meet the 1.3 goalpost based on an interim analysis), you should discuss these plans with FDA before implementation to ensure that FDA agrees that there is sufficient overall exposure to study medication.

Meeting Discussion: ***The sponsor clarified that even after the 1.3 goalpost is met, the study will continue until a minimum of 550 events are captured; this should result in a median study duration of 2 years. The Division stated that this is acceptable.***

The sponsor sought confirmation that the proposed sequence of hypothesis testing is acceptable (specifically, testing the hazard ratio of the secondary MACE [H03] prior to the primary MACE [H04]). The sponsor stated that this approach was chosen because there will be more events in the secondary MACE endpoint, [redacted] (b) (4)

The Division stated that the additional table shell emailed in February pertaining to data presentation for the MACE endpoints is acceptable and sought clarification of which cardiovascular events will be sent for adjudication. The sponsor stated that relevant preferred terms are identified based on an algorithm, investigators are then asked to complete a package for these events, and this package is then forwarded to the [redacted] (b) (4) ***for adjudication. The sponsor agreed to submit the selection algorithm to the Division for review. The sponsor confirmed that the NDA will include explanations for those adverse events that are coded as***

myocardial infarction or stroke based on investigator verbatim terms but that are downgraded by the adjudication committee.

Question 7: Should the Agency find the statistical methodology and fixed, pre-specified order acceptable (b) (4)

FDA Preliminary Response: It is premature at this point to answer Question 7, as labeling will be a review issue.

Meeting Discussion: There was no discussion.

Question 8: A table of contents of the proposed tables, listings, and figures to be included in the interim analysis for Study 402 is also provided in Appendix C. Does the Agency agree with the proposed data presentations planned for the alogliptin and alogliptin/pioglitazone FDC resubmissions?

FDA Preliminary Response: When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) from the interim analysis of Study 402 in addition to the required renal safety analysis?

Meeting Discussion: The sponsor clarified that all adverse event data will be submitted. The laboratory data submitted will be consistent with the information presented in the integrated analysis of safety. The Division agreed that this is acceptable.

The Division sought clarification on how data integrity will be maintained once the 1.8 goalpost is met given the meeting package's description of internal blinded and unblinded teams. The sponsor clarified that they have experience in this area (i.e. study OPI-004) and have detailed Standard Operating Procedures that cover splitting the internal team into a blinded and an unblinded team. Unblinded team members will not cross back to the blinded team or vice versa. Firewalls protect the data. Systems can be reviewed to see who accessed data when. The Data Monitoring Committee is an independent committee. The Division agreed that this is acceptable.

Question 9: Does the Agency agree that the proposed integrated analysis as described in the SAP and the table shells are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify whether the integrated analysis of cardiovascular safety from the controlled Phase 2 and Phase 3 studies, as described in Appendix E, excludes the results from Study 402, the dedicated cardiovascular study. However, we note that it is also acceptable to conduct two analyses, one with and one without Study 402.

Meeting Discussion: ***The sponsor clarified that CV safety will be reviewed in study 402 alone and in Study 402 and all other controlled phase 2-3 trials combined. The sponsor does not plan to conduct a MACE analysis of phase 2-3 trials excluding Study 402, as the remaining trials likely have too few events (~30-40) to determine CV safety. Furthermore, the CV events for most of the phase 2-3 trials, excluding the newly completed trials, were reviewed in the previous NDA submission. The Division agreed with the sponsor's proposed approach.***

Question 10: Does the Agency agree that the proposed analyses and table shells are appropriately designed to assess the long-term safety of alogliptin?

FDA Preliminary Response: For all analyses of duration of exposure (e.g., Table 8.4.2.6), please also present one-year data using a cutoff of 365 days.

Meeting Discussion: ***The sponsor clarified that 335 days refers to the lower bound of the definition of one year (i.e. 365±30 days) based on the window for the 1-year clinic visit. As subjects do not always present themselves for study visits at precisely 1 year (365 days), this definition is used. It is the same definition used in the previous NDA submissions. Furthermore, the sponsor's estimate that there will be controlled data for 500 patients with at least 1-year exposure to alogliptin is based on this definition.***

The Division agreed that this definition is acceptable for meeting the 1-year exposures requested in the Complete Response Letter. However, the Division requested that the sponsor also calculate exposure at ≥365 days. The sponsor agreed.

Question 11: Does the Agency agree with Takeda's definitions for the special interest adverse events?

FDA Preliminary Response: No, we do not agree. Please also do the following:

- **Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.**
- **In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.**
- **For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).**

Meeting Discussion: ***The sponsor agreed to broaden its definition of PCDR to include skin ulcer-related events (bullet #1) and to submit the new list of preferred terms for review.***

Regarding bullet #2, the sponsor clarified that serum amylase and pancreatitis data are only routinely collected in study 402. These data will be submitted. Laboratory and imaging data in confirmed cases of pancreatitis (including those cases occurring in the other studies) will also be submitted.

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor agreed to analyze all available data. The Division agreed with this approach.

Question 12: Does the Agency agree with types of narratives that Takeda proposes to include in the NDA resubmissions?

FDA Preliminary Response: Yes, we agree. Please provide links to the narratives in the study reports from summary tables and line listings.

Meeting Discussion: ***There was no discussion.***

Question 13: Does the Agency find this submission plan acceptable and agree that submitting patient profiles in the NDA resubmissions is not necessary?

FDA Preliminary Response: Yes, we agree with your plan to submit patient narratives for the events agreed to in question 12 (b) (4)

Meeting Discussion: ***There was no discussion.***

Question 14: Does the Agency agree with Takeda's proposal to not manufacture alogliptin/pioglitazone FDC dose strengths that contain alogliptin 6.25 mg and agree that the product labeling can appropriately address dosing patients with severe renal impairment through co-administration of alogliptin and pioglitazone tablets?

FDA Preliminary Response: Yes, we agree.

Meeting Discussion: ***The sponsor sought clarification that the Division agrees with the sponsor's justification and plan to not manufacture alogliptin+pioglitazone FDC tablets using alogliptin 6.25 mg because of <2% expected use of a FDC product that contains this dosage strength. The Division agreed.***

The sponsor asked if they need to address this issue further in the NDA resubmission. The Division stated that it is acceptable to refer to the agreement reached in these meeting minutes.

Question 15: Does the Agency agree that the proposed analyses and table shells for the IAS and interim analysis are appropriately designed to evaluate the safety of alogliptin in subjects with renal impairment?

FDA Preliminary Response: The analyses and proposed data presentation are acceptable.

Meeting Discussion: There was no discussion.

Question 16: With regard to the analysis of adverse events by baseline and endpoint renal status for the IAS and final analysis for Study 402, Takeda defines endpoint renal status as the subject's renal status at the time of last renal assessment. Therefore, for this analysis adverse events will be summarized according to renal impairment (normal, mild, moderate, and severe or ESRD) at Baseline and according to renal impairment at the last renal assessment. Does the Agency agree with this definition of endpoint for this analysis?

FDA Preliminary Response: The proposed analyses are acceptable.

Meeting Discussion: There was no discussion.

Question 17: In the FDA Advice/Information Request letter dated 15 July 2009 regarding Study 402, the Agency stated that if a substantial percentage of patients experience a change in severity status during the course of the study, a secondary analysis should be conducted by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured. Takeda would like clarification on what percentage of patients experiencing a change in severity status during the course of the study would require Takeda to conduct the analysis based on renal severity status at endpoint for the final analysis.

FDA Preliminary Response: If ≥25% of patients experience a change in severity status during the course of the study, you should conduct the analysis based on renal severity status at endpoint for the final analysis.

Meeting Discussion: The sponsor clarified that this analysis will be based on changes between two groups (normal/mild renal impairment vs. moderate/severe renal impairment). This approach is consistent with the randomized strata. The Division agreed to this approach.

Question 18: Does the Agency agree with Takeda's proposal [redacted] (b) (4)

FDA Preliminary Response: No, we do not agree. The proposal [redacted] (b) (4) **will be a review issue.**

(b) (4)

(b) (4)

Meeting Discussion: ***There was no discussion.***

Question 20: Similar to the review timelines described in the Guidance document, Good Review Management Principles and Practices for PDUFA Products, Takeda would like to confirm that the Agency will plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

FDA Preliminary Response: Should results from your application support approval, we plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Meeting Discussion: ***There was no discussion.***

Question 21: If the alogliptin and alogliptin/pioglitazone NDA resubmissions are submitted simultaneously, Takeda would like to confirm that a concurrent action will be taken by the Agency on both of these applications.

FDA Preliminary Response: If both NDAs are resubmitted at the same time, they will be on the same review clock and will have the same user fee goal date. A concurrent action is likely, but the possibility exists that the actions taken will not be concurrent.

Meeting Discussion: There was no discussion.

Question 22: Takeda would like to obtain feedback regarding the need for an Advisory Committee meeting in light of the 6-month review cycle for Complete Response Submissions and the Agency's prior full review of alogliptin. Can the Agency comment at this time if an Advisory Committee meeting will be necessary?

FDA Preliminary Response: This decision will be made after the resubmission of these NDAs.

Meeting Discussion: There was no discussion.

Question 23: If Takeda notifies the Agency 4 months prior to submitting the NDA resubmissions, would the Agency be willing to initiate the process for re-review of 'Nesina' and (b) (4) at that time? If the Agency agrees with this proposal, would the Agency be able to conduct the re-review and confirm the acceptability of the proprietary names within a reasonable timeframe (e.g. 4 weeks)?

Note: The proposed proprietary names, 'Nesina' for alogliptin and (b) (4) for alogliptin/pioglitazone FDC, were found acceptable by the Agency during the first-cycle review of the alogliptin and A/P NDAs, although they must be re-reviewed following the NDA resubmissions of both applications.

FDA Preliminary Response: The Division of Medication Error Prevention and Analysis (DMEPA) reviews trade names. You should submit a request for trade name review when the complete response is submitted. DMEPA's review timeline is 90 days from the date the request is received.

Meeting Discussion: The Division explained that re-review of the previously proposed trade names is automatically conducted during the review cycle upon receipt of the NDA resubmission(s).

Question 24: If Takeda decides to pursue different trade names for alogliptin and/or the A/P FDC product for launch, could Takeda submit such names for the Office of Surveillance and Epidemiology (OSE) to review and approve? For trade names that are subject of an NDA resubmission, what are the internal timelines associated with its review and approval?

FDA Preliminary Response: In the NDA resubmission, you may submit two different trade names for DMEPA to review. DMEPA's review timeline is 90 days from the date they receive the request. This review is generally finalized 90 days prior to the action date. If you wish to pursue alternate names, you will need to withdraw the names that were found to be conditionally acceptable and submit a request for review of the alternate names. This review will follow the same timelines as above.

Please also refer to the Guidance for Industry entitled "*Contents of a Complete Submission for the Evaluation of Proprietary Names*" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Meeting Discussion: The Division explained that submissions requesting trade name review should be submitted directly to the attention of the Office of Surveillance and Epidemiology. If the sponsor chooses to submit new trade names prior to the resubmission in response to the Complete Response letters, the review will follow the IND review timeline (i.e. 180 days).

Question 25: Does Agency agree that the pediatric clinical studies as described above will satisfy the requirements of PREA for alogliptin?

FDA Preliminary Response: We cannot comment on whether or not your proposed pediatric study will satisfy the requirements of PREA until the NDA is resubmitted and your proposal is discussed with the Pediatric Review Committee (PeRC). However, we have some concerns with your proposed Phase 3 pediatric study such as:

(b) (4)

[redacted]

Meeting Discussion: ***The sponsor understood that the Division cannot comment on whether or not the proposed pediatric study will satisfy PREA requirements.*** (b) (4) ***The Division stated that our general approach has been to study new antidiabetic therapies both as monotherapy and as add-on to metformin. The Division also stated that it is unlikely that these pediatric studies will yield useful information on beta-cell preservation.***

Question 26: Takeda would also like to obtain feedback from the Agency regarding the utility of the proposed pediatric plan to qualify for exclusivity under the Best Pharmaceuticals for Children Act (BPCA). A revised Proposed Pediatric Study Request under Section 505A and BPCA will be submitted under separate cover following approval.

FDA Preliminary Response: We cannot enter into an agreement regarding a written request until after NDA approval.

Meeting Discussion: ***There was no discussion.***

Other FDA Comments:

1. When presenting changes from baseline in laboratory parameters (e.g., Table 15.3.4.5.2) include change from baseline to the last available on-treatment measurement (intent-to-treat with last-observation-carried-forward)

Meeting Discussion: ***The sponsor agreed.***

2. It appears that the integrated analyses will use MedDRA version 12.0. If earlier versions of MedDRA were used for the individual study reports, include a table showing those preferred terms that were coded to new preferred terms as a result of the MedDRA version change.

Meeting Discussion: ***The sponsor agreed.***

Additional discussion: The sponsor currently has 50 subjects enrolled in study 402 in the United States. The sponsor plans to respond to the Complete Response letters to the NDAs in 2012.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEHREEN HAI
03/16/2010

From: Hai, Mehreen
To: "Idemoto, Christie Ann (TGRD)";
Subject: RE: IND 69,707/NDA 22-271 Alogliptin - Status Update
Date: Wednesday, May 05, 2010 1:59:50 PM

Hi again Christie,
Regarding your suggested revisions to the FDA meeting minutes for the End-of-Review meeting for NDA 22-271 (alogliptin) and NDA 22-426 (alogliptin-pioglitazone FDC), that you submitted on April 13, 2010, we accept your suggested revisions, and will update our meeting minutes accordingly.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Tuesday, May 04, 2010 6:13 PM
To: Hai, Mehreen
Subject: RE: IND 69,707/NDA 22-271 Alogliptin - Status Update

Thank you, Mehreen.

Christie Ann Idemoto
☎ Office: 847.582.3506 Cell: (b) (6)

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Tuesday, May 04, 2010 1:08 PM
To: Idemoto, Christie Ann (TGRD)
Subject: RE: IND 69,707/NDA 22-271 Alogliptin - Status Update

Hi Christie,
Will get back to you within a day or so with responses to both.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Monday, May 03, 2010 1:30 PM
To: Hai, Mehreen
Subject: IND 69,707/NDA 22-271 Alogliptin - Status Update

Hi Mehreen,

Hope all is well.
I am writing to follow-up on a few pending items. Do you have an estimated timeframe as to when TGRD can expect a response from the Division regarding the following?

1. TGRD's request to use of a different MDRD formulation for patients enrolled in sites in Japan (see email trail below)
2. TGRD's comments/suggested revisions to official minutes from Feb 23 Type B meeting (refer to amendment to NDA 22-271 and NDA 22-426, dated April 13, 2010)

Please let me know if you have any questions.

Thanks very much,

Christie

Christie Ann Idemoto
☎ Office: 847.582.3506 Cell: (b)(6)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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/s/

MEHREEN HAI
05/05/2010

From: Hai, Mehreen
To: "Idemoto, Christie Ann (TGRD)";
Subject: RE: alogliptin NDA 22-271: follow-up on March 15 submission
Date: Tuesday, April 20, 2010 2:39:47 PM

Hi Christie,
We have finished reviewing the lists of PT terms that were submitted on March 15, 2010, and have found them acceptable.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Tuesday, April 13, 2010 5:42 PM
To: Hai, Mehreen
Subject: RE: alogliptin NDA 22-271: follow-up on March 15 submission

Hi Mehreen,

I apologize for the confusion. Let me try to clarify – there are two reasons new terms have been added to the skin reaction PT list:

1. New terms added as a result of versioning from MedDRA 10.0 (version used for the original NDA) to MedDRA 12.1
    - These terms are highlighted in yellow <u>and</u> listed as NEW in the attached.

2. New terms added as result of the Division's recommendation to include terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue
    - These terms are listed as NEW (<u>but not highlighted in yellow</u>) in the attached.

If you still need further clarification or have additional questions, please contact me directly. I am happy to discuss by phone.

Thanks,
Christie

____
Christie Ann Idemoto
(Office: 847.582.3506 Cell: (b) (6)

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Tuesday, April 13, 2010 10:41 AM
To: Idemoto, Christie Ann (TGRD)
Subject: RE: alogliptin NDA 22-271: follow-up on March 15 submission

Hi Christie,
We should be able to review the PT terms in another week or so. But we are a little bit confused about which of the PT terms are recently added, that we need to particularly focus on. Can you please clarify that?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073

Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Friday, April 09, 2010 11:34 AM
To: Hai, Mehreen
Subject: FW: alogliptin NDA 22-271: follow-up on March 15 submission

Hi Mehreen,

Do you have a status update on the Division's review of the attached lists of PT terms?

Any questions, please let me know.

Thanks,
Christie

_____
Christie Ann Idemoto
(Office: 847.582.3506 Cell: (b) (6)

From: Idemoto, Christie Ann (TGRD)
Sent: Wednesday, March 24, 2010 2:32 PM
To: Hai, Mehreen
Subject: alogliptin NDA 22-271: follow-up on March 15 submission

Dear Mehreen,

Thank you very much for sending Takeda the FDA's meeting minutes from our February 23 Type B meeting. We are currently reviewing the minutes in detail and will advise you if we have any significant differences in understanding.

On March 15, 2010, we submitted TGRD's Type B meeting minutes to NDA 22-271; and, in addition (based on action items from the Type B meeting), the following were also provided for FDA's review and comment:

- List of MedDRA PT Terms for PCDR analysis
- List of MedDRA PT Terms for CEC adjudication

Please let me know when we can expect FDA to complete their review of the above PT lists. I have attached these PT lists + submission cover letter to this email for ease of review.

Any questions, please let me know.

Thanks very much in advance,

Christie

_____
Christie Ann Idemoto
Associate Director, Regulatory Affairs
Takeda Global Research & Development Center, Inc.
+ 675 N. Field Drive, Lake Forest, IL 60045
(Office: 847.582.3506
Cell: (b) (6)
* Email: cidemoto@tgrd.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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/s/

MEHREEN HAI
04/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets and for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on February 23, 2010. The purpose of the meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Review Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Review
Meeting Date and Time:	February 23, 2010, 1:30 PM – 2:30 PM (Eastern)
Meeting Location:	White Oak Campus, Building 22, Silver Spring, MD
Application Number:	NDA 022271 and NDA 022426
Product Name:	Nesina (alogliptin) Tablets and (b) (4) (alogliptin/pioglitazone FDC) Tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Valerie Pratt, M.D.
Meeting Recorder:	Mehreen Hai, Ph.D.

FDA ATTENDEES

Curtis Rosebraugh, M.D., M.P.H.	Director, Office of Drug Evaluation II (ODE II)
Mary Parks, M.D.	Director, Division of Metabolic and Endocrinology Products (DMEP)
Hylton Joffe, M.D., M.M.Sc.	Diabetes Team Leader, DMEP
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology II
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Statistics Reviewer, Division of Biometrics II
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Linda Galgay, R.N.	Regulatory Project Manager, DMEP
Arlet Nedeltcheva-Peneva, M.D.	Clinical Reviewer, DMEP

SPONSOR ATTENDEES

Thomas Strack, M.D.	Vice President, Clinical Science
Penny Fleck, M.T.	Director, Clinical Science
Neila Smith, M.D.	Senior Medical Director, Pharmacovigilance
Michie Hisada, M.D.	Medical Director, Pharmacovigilance
Craig Wilson, Ph.D.	Principal Statistician, Biostatistics
Vipin Arora, Ph.D.	Associate Director, Biostatistics
Dan Bollinger, R.Ph.	Principal Scientist, Pharmaceutical Science

Rebecca Adams	Assistant Project Director, Project Management
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Sangeeta Gupte, Ph.D.	Manager, Regulatory Affairs
Christie Idemoto, M.S.	Associate Director, Regulatory Affairs
Yukari Nishikata	Senior Director, Takeda Japan Liaison
Riccardo Camisasca, M.D.	Medical Director, Clinical Science (Europe)

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 21-073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009 for NDA 022426.

The purpose of this meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

2. DISCUSSION

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the Sponsor on February 20, 2010, follow in bold. A summary of the meeting discussion is shown in italicized bold font.

Question 1: Does the Agency agree with the proposed structure and contents of both NDA resubmissions?

FDA Preliminary Response: Yes, but with exceptions noted in the comments below.

Meeting Discussion: There was no discussion.

Question 2: Does the Agency agree with Takeda's plan to summarize all integrated safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Please clarify. Does the question only pertain to the location of the integrated safety data or are you proposing to present these data differently?

Clarify why you are not including Study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the alogliptin/pioglitazone fixed-dose combination NDA.

Meeting Discussion: ***The sponsor clarified that the question pertains only the location of the integrated safety data.***

Study 009 will not be included in the integrated safety analysis for the fixed-dose combination (FDC) product because these subjects were on a thiazolidinedione (TZD) for months to years before starting alogliptin, whereas the subjects in the proposed integrated analysis will be randomized to simultaneously start alogliptin + pioglitazone. Study 009 was not included in the integrated analyses of the original NDAs for the same reason. The Division concurred that it is acceptable to not include Study 009 in the integrated analysis for the FDC product in the Complete Response.

Question 3: For the Safety Updates, Takeda plans to summarize relevant safety data (adverse events, SAEs, and adverse events leading to discontinuation) from the individual Japanese studies within Module 2.7.4 and provide the final clinical study reports for these non-IND studies in Module 5. Does the Agency find this approach acceptable?

FDA Preliminary Response: Yes, this is acceptable. Please cite the table numbers in the original study reports and provide hyperlinks where possible.

Meeting Discussion: ***There was no discussion.***

Question 4: Does the Agency agree that the proposed integrated analyses of the phase 2 and 3 controlled studies as described in the SAPs, and the table shells are adequately designed to address the Agency's requests in Complete Response letters for the both alogliptin alogliptin/pioglitazone safety updates?

FDA Preliminary Response: Yes, but with the following caveats:

- **Please also summarize duration of exposure to study medication according to baseline renal function (mild, moderate, and, severe renal impairment as calculated by both the Cockcroft-Gault and MDRD formulae).**
- **You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline) because such an increase in serum creatinine even within the reference range may reflect an important decline in renal function. If you wish to also analyze renal data with the revised definition, you may do so.**
- **Please clarify if adverse events will be summarized in the pooled study population and by individual study (including recently completed studies).**

Meeting Discussion: ***The sponsor agreed to bullets #1-2. The sponsor stated that adverse events will be summarized by pooled study population and in the newly completed individual studies. Hyperlinks will be provided to adverse events in the study reports submitted with the original NDAs. The Division stated that this approach is acceptable.***

Question 5: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, these are acceptable.

Meeting Discussion: ***There was no discussion.***

Question 6: Does the Agency agree that the proposed primary and secondary MACE analyses as described in the SAP and the table shells for Study 402 are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify the minimum duration of treatment exposure for all patients enrolled in Study 402. If you intend to prematurely terminate Study 402 (e.g., if you meet the 1.3 goalpost based on an interim analysis), you should discuss these plans with FDA before implementation to ensure that FDA agrees that there is sufficient overall exposure to study medication.

Meeting Discussion: ***The sponsor clarified that even after the 1.3 goalpost is met, the study will continue until a minimum of 550 events are captured; this should result in a median study duration of 2 years. The Division stated that this is acceptable.***

The sponsor sought confirmation that the proposed sequence of hypothesis testing is acceptable (specifically, testing the hazard ratio of the secondary MACE [H03] prior to the primary MACE [H04]). The sponsor stated that this approach was chosen because there will be more events in the secondary MACE endpoin (b) (4)

The Division stated that the additional table shell emailed in February pertaining to data presentation for the MACE endpoints is acceptable and sought clarification of which cardiovascular events will be sent for adjudication. The sponsor stated that relevant preferred terms are identified based on an algorithm, investigators are then asked to complete a package for these events, and this package is then forwarded to the (b) (4) ***for adjudication. The sponsor agreed to submit the selection algorithm to the Division for review. The sponsor confirmed that the NDA will include explanations for those adverse events that are coded as***

myocardial infarction or stroke based on investigator verbatim terms but that are downgraded by the adjudication committee.

Question 7: Should the Agency find the statistical methodology and fixed, pre-specified order acceptable (b) (4)

FDA Preliminary Response: It is premature at this point to answer Question 7, as labeling will be a review issue.

Meeting Discussion: There was no discussion.

Question 8: A table of contents of the proposed tables, listings, and figures to be included in the interim analysis for Study 402 is also provided in Appendix C. Does the Agency agree with the proposed data presentations planned for the alogliptin and alogliptin/pioglitazone FDC resubmissions?

FDA Preliminary Response: When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) from the interim analysis of Study 402 in addition to the required renal safety analysis?

Meeting Discussion: The sponsor clarified that all adverse event data will be submitted. The laboratory data submitted will be consistent with the information presented in the integrated analysis of safety. The Division agreed that this is acceptable.

The Division sought clarification on how data integrity will be maintained once the 1.8 goalpost is met given the meeting package's description of internal blinded and unblinded teams. The sponsor clarified that they have experience in this area (i.e. study OPI-004) and have detailed Standard Operating Procedures that cover splitting the internal team into a blinded and an unblinded team. Unblinded team members will not cross back to the blinded team or vice versa. Firewalls protect the data. Systems can be reviewed to see who accessed data when. The Data Monitoring Committee is an independent committee. The Division agreed that this is acceptable.

Question 9: Does the Agency agree that the proposed integrated analysis as described in the SAP and the table shells are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify whether the integrated analysis of cardiovascular safety from the controlled Phase 2 and Phase 3 studies, as described in Appendix E, excludes the results from Study 402, the dedicated cardiovascular study. However, we note that it is also acceptable to conduct two analyses, one with and one without Study 402.

Meeting Discussion: ***The sponsor clarified that CV safety will be reviewed in study 402 alone and in Study 402 and all other controlled phase 2-3 trials combined. The sponsor does not plan to conduct a MACE analysis of phase 2-3 trials excluding Study 402, as the remaining trials likely have too few events (~30-40) to determine CV safety. Furthermore, the CV events for most of the phase 2-3 trials, excluding the newly completed trials, were reviewed in the previous NDA submission. The Division agreed with the sponsor's proposed approach.***

Question 10: Does the Agency agree that the proposed analyses and table shells are appropriately designed to assess the long-term safety of alogliptin?

FDA Preliminary Response: For all analyses of duration of exposure (e.g., Table 8.4.2.6), please also present one-year data using a cutoff of 365 days.

Meeting Discussion: ***The sponsor clarified that 335 days refers to the lower bound of the definition of one year (i.e. 365±30 days) based on the window for the 1-year clinic visit. As subjects do not always present themselves for study visits at precisely 1 year (365 days), this definition is used. It is the same definition used in the previous NDA submissions. Furthermore, the sponsor's estimate that there will be controlled data for 500 patients with at least 1-year exposure to alogliptin is based on this definition.***

The Division agreed that this definition is acceptable for meeting the 1-year exposures requested in the Complete Response Letter. However, the Division requested that the sponsor also calculate exposure at ≥365 days. The sponsor agreed.

Question 11: Does the Agency agree with Takeda's definitions for the special interest adverse events?

FDA Preliminary Response: No, we do not agree. Please also do the following:

- **Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.**
- **In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.**
- **For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).**

Meeting Discussion: ***The sponsor agreed to broaden its definition of PCDR to include skin ulcer-related events (bullet #1) and to submit the new list of preferred terms for review.***

Regarding bullet #2, the sponsor clarified that serum amylase and pancreatitis data are only routinely collected in study 402. These data will be submitted. Laboratory and imaging data in confirmed cases of pancreatitis (including those cases occurring in the other studies) will also be submitted.

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor agreed to analyze all available data. The Division agreed with this approach.

Question 12: Does the Agency agree with types of narratives that Takeda proposes to include in the NDA resubmissions?

FDA Preliminary Response: Yes, we agree. Please provide links to the narratives in the study reports from summary tables and line listings.

Meeting Discussion: ***There was no discussion.***

Question 13: Does the Agency find this submission plan acceptable and agree that submitting patient profiles in the NDA resubmissions is not necessary?

FDA Preliminary Response: Yes, we agree with your plan to submit patient narratives for the events agreed to in question 12 (b) (4)

Meeting Discussion: ***There was no discussion.***

Question 14: Does the Agency agree with Takeda's proposal to not manufacture alogliptin/pioglitazone FDC dose strengths that contain alogliptin 6.25 mg and agree that the product labeling can appropriately address dosing patients with severe renal impairment through co-administration of alogliptin and pioglitazone tablets?

FDA Preliminary Response: Yes, we agree.

Meeting Discussion: ***The sponsor sought clarification that the Division agrees with the sponsor's justification and plan to not manufacture alogliptin+pioglitazone FDC tablets using alogliptin 6.25 mg because of <2% expected use of a FDC product that contains this dosage strength. The Division agreed.***

The sponsor asked if they need to address this issue further in the NDA resubmission. The Division stated that it is acceptable to refer to the agreement reached in these meeting minutes.

Question 15: Does the Agency agree that the proposed analyses and table shells for the IAS and interim analysis are appropriately designed to evaluate the safety of alogliptin in subjects with renal impairment?

FDA Preliminary Response: The analyses and proposed data presentation are acceptable.

Meeting Discussion: There was no discussion.

Question 16: With regard to the analysis of adverse events by baseline and endpoint renal status for the IAS and final analysis for Study 402, Takeda defines endpoint renal status as the subject's renal status at the time of last renal assessment. Therefore, for this analysis adverse events will be summarized according to renal impairment (normal, mild, moderate, and severe or ESRD) at Baseline and according to renal impairment at the last renal assessment. Does the Agency agree with this definition of endpoint for this analysis?

FDA Preliminary Response: The proposed analyses are acceptable.

Meeting Discussion: There was no discussion.

Question 17: In the FDA Advice/Information Request letter dated 15 July 2009 regarding Study 402, the Agency stated that if a substantial percentage of patients experience a change in severity status during the course of the study, a secondary analysis should be conducted by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured. Takeda would like clarification on what percentage of patients experiencing a change in severity status during the course of the study would require Takeda to conduct the analysis based on renal severity status at endpoint for the final analysis.

FDA Preliminary Response: If ≥25% of patients experience a change in severity status during the course of the study, you should conduct the analysis based on renal severity status at endpoint for the final analysis.

Meeting Discussion: The sponsor clarified that this analysis will be based on changes between two groups (normal/mild renal impairment vs. moderate/severe renal impairment). This approach is consistent with the randomized strata. The Division agreed to this approach.

Question 18: Does the Agency agree with Takeda's proposal [redacted] (b) (4)

FDA Preliminary Response: No, we do not agree. The proposal [redacted] (b) (4) **will be a review issue.**

(b) (4)

(b) (4)

Meeting Discussion: ***There was no discussion.***

Question 20: Similar to the review timelines described in the Guidance document, Good Review Management Principles and Practices for PDUFA Products, Takeda would like to confirm that the Agency will plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

FDA Preliminary Response: Should results from your application support approval, we plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Meeting Discussion: ***There was no discussion.***

Question 21: If the alogliptin and alogliptin/pioglitazone NDA resubmissions are submitted simultaneously, Takeda would like to confirm that a concurrent action will be taken by the Agency on both of these applications.

FDA Preliminary Response: If both NDAs are resubmitted at the same time, they will be on the same review clock and will have the same user fee goal date. A concurrent action is likely, but the possibility exists that the actions taken will not be concurrent.

Meeting Discussion: There was no discussion.

Question 22: Takeda would like to obtain feedback regarding the need for an Advisory Committee meeting in light of the 6-month review cycle for Complete Response Submissions and the Agency's prior full review of alogliptin. Can the Agency comment at this time if an Advisory Committee meeting will be necessary?

FDA Preliminary Response: This decision will be made after the resubmission of these NDAs.

Meeting Discussion: There was no discussion.

Question 23: If Takeda notifies the Agency 4 months prior to submitting the NDA resubmissions, would the Agency be willing to initiate the process for re-review of 'Nesina' and (b) (4) at that time? If the Agency agrees with this proposal, would the Agency be able to conduct the re-review and confirm the acceptability of the proprietary names within a reasonable timeframe (e.g. 4 weeks)?

Note: The proposed proprietary names, 'Nesina' for alogliptin and (b) (4) for alogliptin/pioglitazone FDC, were found acceptable by the Agency during the first-cycle review of the alogliptin and A/P NDAs, although they must be re-reviewed following the NDA resubmissions of both applications.

FDA Preliminary Response: The Division of Medication Error Prevention and Analysis (DMEPA) reviews trade names. You should submit a request for trade name review when the complete response is submitted. DMEPA's review timeline is 90 days from the date the request is received.

Meeting Discussion: The Division explained that re-review of the previously proposed trade names is automatically conducted during the review cycle upon receipt of the NDA resubmission(s).

Question 24: If Takeda decides to pursue different trade names for alogliptin and/or the A/P FDC product for launch, could Takeda submit such names for the Office of Surveillance and Epidemiology (OSE) to review and approve? For trade names that are subject of an NDA resubmission, what are the internal timelines associated with its review and approval?

FDA Preliminary Response: In the NDA resubmission, you may submit two different trade names for DMEPA to review. DMEPA's review timeline is 90 days from the date they receive the request. This review is generally finalized 90 days prior to the action date. If you wish to pursue alternate names, you will need to withdraw the names that were found to be conditionally acceptable and submit a request for review of the alternate names. This review will follow the same timelines as above.

Please also refer to the Guidance for Industry entitled "*Contents of a Complete Submission for the Evaluation of Proprietary Names*" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Meeting Discussion: The Division explained that submissions requesting trade name review should be submitted directly to the attention of the Office of Surveillance and Epidemiology. If the sponsor chooses to submit new trade names prior to the resubmission in response to the Complete Response letters, the review will follow the IND review timeline (i.e. 180 days).

Question 25: Does Agency agree that the pediatric clinical studies as described above will satisfy the requirements of PREA for alogliptin?

FDA Preliminary Response: We cannot comment on whether or not your proposed pediatric study will satisfy the requirements of PREA until the NDA is resubmitted and your proposal is discussed with the Pediatric Review Committee (PeRC). However, we have some concerns with your proposed Phase 3 pediatric study such as:

(b) (4)

[redacted]

Meeting Discussion: ***The sponsor understood that the Division cannot comment on whether or not the proposed pediatric study will satisfy PREA requirements.*** (b) (4) ***The Division stated that our general approach has been to study new antidiabetic therapies both as monotherapy and as add-on to metformin. The Division also stated that it is unlikely that these pediatric studies will yield useful information on beta-cell preservation.***

Question 26: Takeda would also like to obtain feedback from the Agency regarding the utility of the proposed pediatric plan to qualify for exclusivity under the Best Pharmaceuticals for Children Act (BPCA). A revised Proposed Pediatric Study Request under Section 505A and BPCA will be submitted under separate cover following approval.

FDA Preliminary Response: We cannot enter into an agreement regarding a written request until after NDA approval.

Meeting Discussion: ***There was no discussion.***

Other FDA Comments:

1. When presenting changes from baseline in laboratory parameters (e.g., Table 15.3.4.5.2) include change from baseline to the last available on-treatment measurement (intent-to-treat with last-observation-carried-forward)

Meeting Discussion: ***The sponsor agreed.***

2. It appears that the integrated analyses will use MedDRA version 12.0. If earlier versions of MedDRA were used for the individual study reports, include a table showing those preferred terms that were coded to new preferred terms as a result of the MedDRA version change.

Meeting Discussion: ***The sponsor agreed.***

Additional discussion: The sponsor currently has 50 subjects enrolled in study 402 in the United States. The sponsor plans to respond to the Complete Response letters to the NDAs in 2012.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEHREEN HAI
03/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING GRANTED

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets and for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We also refer to your October 28, 2009, correspondence requesting an End-of-Review conference to discuss and confirm the steps required to support the approvability of NDA 022271 and NDA 022426. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date:	**Tuesday, February 23, 2010**
Time:	**1:30 – 3:00 pm**
Location:	**FDA White Oak Campus, Building 22** **10903 New Hampshire Avenue, Silver Spring, MD 20993**

CDER participants (tentative):

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II (ODE II)
Lee Ripper	Associate Director for Regulatory Affairs, ODE II
Mary Parks, M.D.	Director, Division of Metabolic and Endocrinology Products (DMEP)
Hylton Joffe, M.D.	Diabetes Team Leader, DMEP
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-marketing Assessment I
Sally Choe, Ph.D.	Team Leader, Division of Clinical Pharmacology II
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology II

Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Statistics Reviewer, Division of Biometrics II
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at mehreen.hai@fda.hhs.gov so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Mehreen Hai (796-5073); Penya Littleton (796-1180).

Please notify me at least two weeks prior to the meeting if any of your attendees are NOT U.S. citizens, as additional information will be required.

Provide the background information for the meeting (three copies to the application and **20** desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 22, 2010, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET

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/s/

MEHREEN HAI
12/15/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-426 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, PhD
Product Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Dr. Gupte:

Please refer to your September 19, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We recommend these dissolution conditions: Medium – 900 mL of pH 2.2 Sorensen buffer without deaeration, Apparatus 2, and Paddle rotation speed of 50 rpm.

2. The Q for pioglitazone should be changed (b) (4) to (b) (4) in 30 minutes at 50 rpm.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
6/9/2009 02:59:40 PM

From:	Marchick, Julie
To:	"Gupte, Sangeeta (TGRD)"; "Idemoto, Christie Ann (TGRD)";
CC:	
Subject:	NDA 22-426 Alogliptin/Pioglitazone FDC - Information Request
Date:	Wednesday, May 20, 2009 10:18:32 AM
Attachments:	

Good Morning,

We have two more requests for you.

1. Please calculate the number of subjects exposed to alogiptin+pioglitazone for ≥6, ≥12, and ≥18 months in controlled trials TZD-009, OPI-002, and OPI-001. Please run a second analysis which also includes the uncontrolled data from OLE-012 study 009 subgroup, which was included in the 120-day safety update. Please run a third analysis which also includes the uncontrolled data from OLE-012 study 009, OPI-002, and OPI-001 subgroups.

2. Please clarify why the 120-day safety update "include[d] data from all subjects in study 009 who received at least 1 dose of alogliptin either in study 009 or upon entering study 012 while maintaining concomitant pioglitazone therapy" but did not include data from similar patients in studies OPI-002 and OPI-001.

Let me know if you have any questions.

Thanks,
Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)

julie.marchick@fda.hhs.gov

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/s/

Julie Marchick
5/20/2009 10:21:25 AM
CSO

From:	Marchick, Julie
To:	"Idemoto, Christie Ann (TGRD)"; "Gupte, Sangeeta (TGRD)";
CC:	
Subject:	NDA 22-271 Alogliptin and NDA 22-246 Alogliptin/ Pioglitazone - Information Requests
Date:	Friday, May 01, 2009 8:01:04 AM
Attachments:	

Good Morning Christie and Sangeeta,

We have the following requests. We ask that you submit the requested information by Wednesday, May 6.

1. Please calculate the number of subjects exposed to alogliptin for >= 6, >=12, and >=18 months. Please include subjects in NDA 22-271's controlled phase 2/3 trials and uncontrolled OLE-012 (up to and including the 120 day safety update) as well as subjects exposed to alogliptin in NDA 22-426 controlled phase 2/3 trials (at the time of NDA 22-426 submission). Please run a second analysis which also includes the NDA 22-426 120 day safety update. Please display data for subjects exposed to alogliptin only. As another analysis, please include subjects in the alogliptin+pioglitazone arm(s) in NDA 22-426. For all analyses, present data by alogliptin dose (explain how you handle patients who switched from 12.5 mg to 25 mg) and for combined alogliptin doses.

2. Please rerun the same analyses in (1) above and show the data by category of renal impairment (mild, moderate, or severe renal impairment), using the Cockcroft-Gault method for one analysis and the MDRD formula as another analysis. For these renal analyses, please run one set of analyses including OL-012 and another set of analysis excluding OL-012.

Please let me know if you have any questions.

Thanks,
Julie

Julie Marchick

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

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/s/

Julie Marchick
5/1/2009 08:03:46 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-426 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, PhD
Product Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Gupte:

Please refer to your September 19, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

For the alogliptin benzoate drug substance, the particle size criteria include X_{90} [redacted] (b) (4) Several of the NDA registration batches do not meet this criterion, with values of X_{90} ranging from [redacted] (b) (4) Justify the specification in light of the batch data.

Drug Product

1. Provide additional information regarding operating parameters and in-process controls [redacted] (b) (4)

2. Criteria for related substances is not included the drug product specification. There are not sufficient historical data to justify excluding this test from the fixed-dose combination product specification, particularly for potential alogliptin benzoate related substances. Therefore, add criteria for product-related substances to the drug product specification. We note that you already have a validated analytical procedure for this attribute.

3. Provide additional information [redacted] (b) (4)

4. (b) (4) In future stability studies, include a test (b) (4) in your stability protocol.

5. A shelf life (b) (4) is currently acceptable based upon the stability data provided in your original submission, per ICH Q1E, which specifies that the shelf life can be no more than twice the period covered by long term stability data. We remind you of your commitment to supply a year of long term stability data for all dosage strengths in all packaging configurations, no later than 3 months prior to the PDUFA goal date for this NDA.

6. Revise the packaging labels to add the content of each salt, for example, "Each film-coated tablet contains xx.xx mg of alogliptin benzoate and xx.xx mg of pioglitazone hydrochloride." Revise the Description section and How Supplied section of the full prescribing information with the same changes.

Dissolution Data

1. To grant a biowaiver for the intermediate strengths, dissolution profiles must be generated for all strengths in at least three media (e.g., pH 2.2, 4.5 and 6.8 buffers) demonstrating similarities in dissolution profiles for all strengths in all three media using validated dissolution methods. We recommend that the f2 test be used to compare profiles from the different strengths of the product at each pH. An f2 value > 50 indicates a sufficiently similar dissolution profile such that further in vivo studies are not needed.

2. For alogliptin, provide dissolution data for individual tablets at each time point (5, 10, 15, 20, 30 and 45 minutes) for different lots of each strength in at least three pH mediums (e.g., pH 2.2, 4.5 and 6.8).

3. For pioglitazone, provide dissolution data for individual tablets at each time point (5, 10, 15, 20, 30 and 45 minutes) for different lots of each strength in at least two additional pH mediums (e.g., pH 4.5 and 6.8).

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
4/3/2009 02:15:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-426

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

Takeda Global Research & Development Center, Inc..
ATTENTION: Sangeeta Gupte, PhD
Product Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, Illinois 60045-4832

Dear Dr. Gupte:

Please refer to your New Drug Application (NDA) dated September 19, 2008, received September 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Pioglitazone Tablets, 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.

We also refer to your October 29, 2008, correspondence received October 30, 2008, requesting review of your proposed proprietary name (b) (4) We have completed our review of the proposed proprietary name (b) (4) and have concluded that it is acceptable.

The proposed proprietary name (b) (4) will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 29, 2008, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Millie Wright, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1067. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Julie Marchick, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Enid Galliers
1/28/2009 11:59:46 AM
E. Galliers signing on behalf of M. Parks

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-426

PROPRIETARY NAME REQUEST
ADVICE/ACKNOWLEDGMENT

Takeda Global Research & Development Center, Inc.
ATTENTION: Sangeeta Gupte, Ph.D.
Product Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, Illinois 60045-4832

Dear Dr. Gupte:

Please refer to your New Drug Application (NDA) dated September 19, 2008, received September 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin/pioglitazone fixed-dose combination tablets, 25 mg/15 mg; 25 mg/30 mg; 25 mg/45 mg; 12.5 mg/15 mg; 12.5 mg/30 mg; 12.5 mg/45 mg.

We also refer to your October 29, 2008, correspondence, received October 30, 2008, requesting a review of your proposed proprietary name (b) (4)

We note that you have also included an alternate proposed proprietary name (b) (4) in your submission. We will not initiate review of this alternate name as part of this review cycle. If the proposed proprietary name (b) (4) is denied, we will notify you of this decision. At that time, you must submit a new complete request for review of the alternate name (b) (4)

If you have any questions regarding the contents of this letter or any other aspect of the proprietary name review process, call Mildred Wright, Regulatory Project Manager in the Office of Surveillance and Epidemiology (OSE), at (301) 796-1027. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Julie Marchick, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Enid Galliers
1/27/2009 04:27:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-426

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, PhD
Product Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Gupte:

Please refer to your new drug application (NDA) dated September 19, 2008, received September 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for alogliptin/pioglitazone fixed dose combination tablets.

We also refer to your submissions dated October 29, November 13, and November 14, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **July 22, 2009**.

We are providing the following comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

Chemistry, Manufacturing, and Controls

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. [redacted] (b) (4)

4. Provide a justification [redacted] (b) (4)

5. [redacted] (b) (4)

6. Provide references to the 21 CFR [redacted] (b) (4) regulations for the [redacted] (b) (4) container closure systems used to package the drug substance and drug product.

Statistical

1. As discussed during the October 30, 2008, teleconference, please provide a data file with the country and country code for each investigative site in Study 001 and Study 002.

2. Please provide a summary of the occurrence of rescue within the context of the summary of disposition for Study 001 and Study 002. Examples include:

   - A summary by treatment arm of the percentage of patients who (a) completed the study; (b) discontinued or rescued; with (b) broken down further into (b1) discontinued; (b2) rescued; with (b2) broken down further into (b2i) rescued under fasting plasma glucose criteria from weeks 0-12, and (b2ii) rescued under HbA1c criteria from weeks 12 on.

   - Kaplan-Meier plots of disposition by week on study. For one set of plots, combine "discontinued" and "rescued" patients into the category of "did not complete."

   - A statistical analysis of the incidence of rescue/discontinuation.

   If this information is already available in the current submission, please indicate its location.

Clinical Pharmacology

Please provide the pharmacokinetic parameters for alogliptin and pioglitazone in Study-322OPI-101 and Study-01-06-TL-322OPI-006 as SAS transport files with the parameters containing (but not limited to) the following column headings: Subject ID, Study ID, Analyte, Treatment, Sequence, Period, AUC_{INF}, AUC_{24}, AUC_{TLQC}, C_{max}, T_{max}, Percentage $AUC_{extrapolated}$, $T_{1/2}$, Comments (If any). You may include any other relevant columns in the datasets.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your requests, we will notify you if the requested waiver and deferral have been denied.

Please submit your pediatric drug development plan. Your pediatric drug development plan must include the following:

- a short description of the planned studies,
- the age groups to be studied,
- the date you plan to start enrollment,
- the date you plan to begin the studies,
- the date you expect to complete the studies, and
- the date you expect to submit the study results.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Marchick
12/2/2008 01:38:55 PM
Julie Marchick on behalf of Lina AlJuburi

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-426 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, PhD
Product Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Gupte:

Please refer to your September 19, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin/pioglitazone fixed dose combination tablets.

We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please conduct a Major Adverse Cardiovascular Events (MACE) meta-analysis (cardiovascular death, nonfatal myocardial infarction, and stroke) of all completed Phase 2 and 3 trials of alogliptin + pioglitazone. Please express the data as number of people with events and provide both the total number of randomized patients and the patient-year exposure for the various treatment groups, both by individual study and combined across studies. Please also provide information on the incidence of the endpoint by alogliptin dose and show the numbers both by individual study and pooled. Please calculate the risk ratio with 95% confidence interval for the combined data from placebo-controlled trials and add-on trials (drug vs. placebo, each added to standard therapy).

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
11/5/2008 03:40:52 PM

From:	Marchick, Julie
To:	"sgupte@tgrd.com";
CC:	
Subject:	NDA 22-426 Alogliptin/Pioglitazone - Request for Datasets
Date:	Tuesday, October 28, 2008 8:07:12 AM
Attachments:	

Good Morning Sangeeta,

We request that you submit the following datasets to NDA 22-426, or direct us as to where we can find this information in the electronic submission. If these datasets are not currently available in the submission, we request that you submit them no later than Friday, November 14. Please note that this is a potential refuse to file issue.

For Studies 001 and 002:

1. Provide a dataset with the investigator code, country code and geographic region code for each randomized patient. The datasets DEMO.xpt from the alogliptin NDA 022271 for Studies 007, 008, 009, 010 and 011 are useful examples. If these codes are available in the current submission, please indicate their location.

2. Provide datasets with additional information about the disposition status of each patient who was randomized to the studies. The datasets DS.xpt from the alogliptin NDA 022271 for Studies 007, 008, 009, 010 and 011 are useful examples. At a minimum, these datasets should include variables that identify and code for the following:

- The randomization assignment of each patient
- The status of each patient with respect to randomization, the intention-to-treat population, the per-protocol population, and other analyses populations
- The time on study for each patient

If this information is already available in the current submission, please indicate

its location.

3. Provide analysis datasets for the efficacy endpoints. At a minimum, it would be useful to have these datasets for HbA1c, fasting plasma glucose and body weight. These datasets should be structured to enable us to re-create the analyses of key efficacy endpoints. The datasets EFF.xpt from the alogliptin NDA 022271 for Studies 007, 008, 009, 010 and 011 are useful examples. At a minimum, these datasets should include variables that identify and code for the following:

- The randomization assignment of each patient
- The status of each patient with respect to randomization, the intention-to-treat population, the per-protocol population, and other analyses populations
- Age, gender, race, ethnicity
- Baseline levels of variables used in the analysis of covariance models
- Baseline levels of the efficacy endpoints
- Stratification variables used in the randomization and the analysis models
- Change from baseline levels of the efficacy endpoints
- Visit number and week number
- Code for the visit used for the end of study endpoint for each patient
- Code for the use of LOCF imputation at the end of study endpoint

If this information is already available in the current submission, please indicate its location.

Please let me know if you have any questions.

Thanks,
Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

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/s/

Julie Marchick
10/28/2008 01:30:54 PM
CSO

From: Marchick, Julie
To: Gupte, Sangeeta (TGRD);
Subject: NDA 22-426 Alogliptin/pioglitazone FDC - PLR Format Review
Date: Thursday, October 09, 2008 9:13:15 AM
Attachments: PLR Format Review Comments.pdf

Good Morning Sangeeta,

We have completed the initial format review of your proposed package insert. Please see the attached document listing our comments. We request that you submit a revised proposed package insert by January 15, 2009.

Please contact me if you have any questions.

Thanks,
Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

NDA 22-426 – alogliptin/pioglitazone fixed-dose combination tablets
PLR Format Review

Please address the identified issues and re-submit labeling by January 15, 2009. This updated version of labeling will be used for further labeling discussions.

Highlights

Beginning of Highlights

- Do not use the "TM" or "R" symbols after the drug names in Highlights or in the Table of Contents. You can use these symbols once upon first use in the full prescribing information (FPI). We recommend this because the symbol will not appear in the SPL version of labeling, and we want the Word version to match the SPL version as much as possible.

- Remove [redacted] (b) (4)

Boxed Warning

- The entire boxed warning must be bolded.

- Add the following bolded, italicized statement under "**WARNING: CONGESTIVE HEART FAILURE**":

  See full prescribing information for complete boxed warning.

End of Highlights

- The entire statement "**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**" must be bolded.

Table of Contents

- The statement "**WARNING – CONGESTIVE HEART FAILURE**" must be bolded.

- There is no requirement that the patient package insert (PPI) be a subsection under the Patient Counseling Information section. If the PPI is reprinted at the end of the labeling, include it as a subsection (i.e., 17.3). However, if the PPI is attached (but is intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI is referenced in the Patient Counseling Information section. If the PPI is not a subsection, then it should not be listed in the Table of Contents.

- The statement "Sections or subsections omitted from the full prescribing information are not listed." should not be bolded.

FPI

Throughout FPI

- In the preferred presentation of cross-references in the FPI, the word "see" is italicized. For example, [*See Warnings and Precautions (5.1)*].

Boxed Warning

- The entire boxed warning should be bolded.

6 Adverse Reactions

- The statement, "Because clinical trials are conducted under widely varying conditions…" should be relocated to the beginning of subsection 6.1 Clinical Studies Experience.

(b) (4)

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/s/

Julie Marchick
10/9/2008 09:17:14 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-426

NDA ACKNOWLEDGMENT

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, PhD
Product Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Gupte:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Alogliptin/pioglitazone fixed dose combination tablets

Date of Application: September 19, 2008

Date of Receipt: September 22, 2008

Our Reference Number: NDA 22-426

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 21, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial

(NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,* to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, please call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Marchick
9/29/2008 10:40:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6/2/08

IND 73,193

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, PhD
Program Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Gupte:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SYR-322-4833 (alogliptin plus pioglitazone HCl fixed dose combination) Tablets.

We also refer to your amendment dated May 14, 2008, containing additional clarification regarding three pre-NDA questions that we responded to in our letter dated May 7, 2008. Your original questions 6-8 are repeated below. Our responses provided on May 7, 2008, follow in italics. Your clarifications submitted on May 14, 2008, follow in bold print. Our responses follow in bold italics.

Question 6:

Does the Agency concur with TGRD's plan to analyze and submit any long-term safety data for concomitant use of alogliptin and pioglitazone as part of the NDA for alogliptin; therefore, it would not be necessary to submit a separate 120-day update to the current FDC product NDA?

Division Response: Before we can respond to this question, please clarify the amount and type of anticipated additional safety data that would be available at the time of the 120-day update to the current NDA, if we did not waive such an update. Include in your response, a description of the studies from which the data would be generated and the number of additional patients that would be exposed to concomitant alogliptin and pioglitazone for ≥6 months, ≥1 year, and ≥18 months.

In addition, we note that patients from Studies 001 and 002 may be included in the open label extension study (Study SYR-322-OLE-012), which is submitted under NDA 22-271. Please clarify your comment that continued therapy with a thiazolidinedione (i.e., pioglitazone) is not required in the open label extension study for patients enrolled in Studies 001 and 002 who enroll in Study 012.

TGRD Response: To assist the Division in responding to our initial question, TGRD would like to clarify that the only additional safety data that would be available at the 120-day safety update will come from subjects in the ongoing open-label extension study with alogliptin, Study 012 (SYR-322-OLE-012). Data regarding concomitant alogliptin and pioglitazone exposure will come from subjects who were initially enrolled in Study 009 (SYR-322-TZD-009) and who are currently enrolled in the open-label extension Study 012. Based on data extracted from the alogliptin NDA 120-Day Safety Update submitted on 25 April 2008, we estimate that 377 subjects were exposed to alogliptin and pioglitazone for ≥6 months, 185 subjects were exposed to alogliptin and pioglitazone for ≥12 months, and 76 subjects were exposed to alogliptin and pioglitazone for ≥18 months.

Subjects from Study 009 who chose to rollover into the open-label extension Study 012 were required to continue their thiazolidinedione background therapy during the open-label extension. In contrast, subjects from FDC Studies 001 and 002 could not continue pioglitazone therapy when they rolled into the open-label extension because they had been randomized in a blinded fashion to alogliptin alone, pioglitazone alone, or a combination of both in the FDC studies. It was possible, therefore, that a subject may not have received combination alogliptin and pioglitazone therapy. As a consequence, subjects from the FDC studies, who are currently enrolled in Study 012, would not contribute to long-term exposure of alogliptin and pioglitazone combination.

Division Response: Please clarify the patient exposure numbers for aloglitpin + pioglitazone for ≥6 months, ≥12 months, and ≥18 months, based on the anticipated cutoff date of the safety update for the FDC NDA. If the numbers will be the same as for the alogliptin NDA safety update, submitted on April 25, 2008, then we concur with your proposal not to submit a 120-day safety update for the FDC NDA.

Question 7:

Does the Agency concur with the analysis methodology (including the definition of study groups) detailed in the draft integrated safety and analysis plan?

Division Response: The study grouping is described in Appendix F, page 307, of the meeting package. To summarize, you propose that you will include data from Studies 001 and 002 ("Phase 3 Controlled Studies") in "3 active treatment groupings: SYR-322 Only [alogliptin], Pioglitazone Only, and SYR-322 + Pioglitazone." Please also include subsets of data by dose within these treatment groupings.

Please include an overall summary of data that also includes data from Study 009 (alogliptin and pioglitazone combination therapy), which was submitted in NDA 22-271, as well as data from Studies 001 and 002, which will be submitted in the proposed NDA.

The Subgroups Used in Data Presentations are summarized in Table 3.a. (page 309 of meeting package). Please also include data for subgroups of glomerular filtration rate, as estimated by the Cockcroft-Gault and MDRD equations, and data for subgroups of urinary albumin/creatinine ratio (if these data are available).

Division's Additional Comment: Please provide the number of patients included in this FDC NDA who will be exposed to both alogliptin and pioglitazone (by dose of each drug, and by

study) for one year or longer. Include the number of patients who are enrolled in the open-label study from Studies 001, 002, and 009.

TGRD Response: TGRD would like to clarify further the presentation of the integrated safety data using 3 treatment groupings. The primary purpose of the safety presentation is to evaluate the overall safety of the combination of alogliptin and pioglitazone compared to alogliptin or pioglitazone alone. This was the basis for choosing the presentation of 3 treatment groupings (ie, all alogliptin, all pioglitazone, and FDC). Since 2 doses of alogliptin (12.5 and 25 mg) and 3 doses of pioglitazone (15, 30, and 45 mg) were evaluated in different combinations, with limited overlap between the treatment combinations in the 2 FDC studies, the individual clinical study reports were considered the appropriate place to discuss the different doses of each agent. With this clarification, we would like to obtain agreement from the Division on this approach.
In response to the Division's request to provide an integrated summary of data from Studies 001, 002, and 009, TGRD would like to clarify our plan to discuss Study 009 separately from the integrated FDC studies. Study 009 evaluated 12.5 and 25 mg of alogliptin in subjects previously treated with a thiazolidinedione (ie, naïve only to alogliptin); whereas, the subjects from the FDC studies had no previous exposure to either pioglitazone or alogliptin. Because the expected adverse event profiles in these 2 populations would be different based on the different lengths of exposure to pioglitazone, TGRD considered it appropriate to discuss Study 009 separate from the FDC studies. TGRD concludes that providing separate analyses of these 2 populations as part of the NDA will enable the Division to fully assess the safety of the combination of alogliptin with pioglitazone as well as the addition of alogliptin to background pioglitazone therapy. TGRD would appreciate the Division's comment on this approach.

TGRD acknowledges the Division's comments regarding inclusion of data for subgroups of glomerular filtration rate as estimated by the Cockcroft-Gault and MDRD equations, and urinary albumin/creatinine ratio. TGRD will provide these analyses, which will be similar to those submitted in response to the April 18 Information Request (Sequence 0007, dated May 9, 2008) received for the alogliptin NDA 22-271.

The TGRD response to 'Division's Additional Comment' in regard to the number of patients included in this FDC NDA who will be exposed to both alogliptin and pioglitazone is provided in the response to Question 6.

Division Response: We agree with your proposed approaches for the presentation of the integrated safety data and for discussing Study 009 separately from the FDC studies.

Question 8:
Does the FDA agree that the planned efficacy data presentation, as proposed in the briefing document, for Section 2.7.3 Summary of Clinical Efficacy of the NDA is appropriate and adequate to support the Agency's review of efficacy data?

Division Response: Yes. It appears appropriate. For study 001, please perform the comparisons of FDC to components alone only when the primary analysis for the given FDC dose is significant. Also, please include a dose response surface analysis as a supportive analysis. For

Study 002, please compare the 12.5 mg alogliptin+30 mg pioglitazone to the 25 mg alogliptin alone group as an exploratory analysis.

TGRD Response: Results from FDC Studies 001 and 002 were reported in April and May 2008. TGRD would like to clarify with the Division that the requested analyses (Study 001 surface analysis and Study 002 exploratory analysis) will therefore be performed as post-hoc analyses and provided as part of the NDA.

Division Response: This is acceptable.

If you have any questions, contact Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 73193	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	SYR-322-4833(PIOGLITAZONE HCL)TABLETS

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/s/

MARY H PARKS
06/02/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 73,193

5/7/08

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, Ph.D.
Program Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Dr. Gupte:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SYR-322-4833 (alogliptin plus pioglitazone HCl fixed-dose combination) Tablets.

We also refer to your amendment dated January 23, 2008, containing a request for a Type B Pre-New Drug Application (Pre-NDA) meeting. The meeting request was denied, but we are providing responses to the questions included in your February 15, 2008, briefing document. Your questions are repeated below and our responses follow in bold print.

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.

Nonclinical

3. Does the FDA agree that the compound specific nonclinical program for alogliptin and pioglitazone, along with the 13-week toxicity study and the embryo-fetal toxicity study with alogliptin and pioglitazone in combination will adequately support the filing and approval of the marketing application?

   Division Response: Yes, we agree that the combination toxicology and embryofetal toxicology studies support the nonclinical component for filing (but not approval) of the NDA. The approval will be based on FDA review of the submitted data.

Clinical

4. Does the FDA agree that the pharmacokinetic programs and the drug interaction programs for single-agents will adequately support the specific label statements for the FDC product?

   Division Response: Based on what you have submitted, it seems that the pharmacokinetic programs and the drug interaction programs for single-agents will likely support the registration of the FDC product. However, the specific label

statements will depend on the review of the studies you will submit in the proposed NDA as well as the studies that are currently under review in NDA 22-271 (alogliptin).

5. Based on the previous agreements gained through the meetings, protocol review, and comments, does the Agency agree that the data packages for the studies described above will adequately support the proposed indications for the FDC product?

   Division Response: Yes, we agree that the proposed data packages will support the proposed FDC product (fixed dose combination product of alogliptin and pioglitazone) for the treatment of type 2 diabetes mellitus. We note, however, that approval will be based on review of these studies as well as those submitted in the NDA for alogliptin (NDA 22-271). In addition, please note we have simplified the indication for type 2 diabetes mellitus in the prescribing information. The new indication for a FDC product for type 2 diabetes is "FDC PRODUCT is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both COMPONENT A and COMPONENT B is appropriate". Relevant efficacy and safety information from the clinical pharmacology studies and supportive clinical trials wills be included in the pertinent portions of the label.

   Also, the Division is no longer granting "initial treatment" indications for drugs and biologics developed for the treatment of type 2 diabetes. Reasons for this approach include (a) the lack of data showing long-term benefit of using one initial treatment strategy over another, (b) our desire to not encourage initial therapy with dual agents in treatment-naive patients who may otherwise be successfully treated with a single agent, and (c) our desire to not lock patients into dual therapy, as some patients who start on dual therapy may be able to achieve excellent control with a single agent after the initial hyperglycemia is improved.

6. Does the Agency concur with TGRD's plan to analyze and submit any long-term safety data for concomitant use of alogliptin and pioglitazone as part of the NDA for alogliptin; therefore, it would not be necessary to submit a separate 120-day update to the current FDC product NDA?

   Division Response: Before we can respond to this question, please clarify the amount and type of anticipated additional safety data that would be available at the time of the 120-day update to the current NDA, if we did not waive such an update. Include in your response, a description of the studies from which the data would be generated and the number of additional patients that would be exposed to concomitant alogliptin and pioglitazone for ≥6 months, ≥1 year, and ≥18 months.

   In addition, we note that patients from Studies 001 and 002 may be included in the open label extension study (Study SYR-322-OLE-012), which is submitted under NDA 22-271. Please clarify your comment that continued therapy with a thiazolidinedione (i.e., pioglitazone) is not required in the open label extension study for patients enrolled in Studies 001 and 002 who enroll in Study 012.

Statistics

7. Does the Agency concur with the analysis methodology (including the definition of study groups) detailed in the draft integrated safety and analysis plan?

   Division Response: The study grouping is described in Appendix F, page 307, of the meeting package. To summarize, you propose that you will include data from Studies 001 and 002 ("Phase 3 Controlled Studies") in "3 active treatment groupings: SYR-322 Only [alogliptin], Pioglitazone Only, and SYR-322 + Pioglitazone."

   Please also include subsets of data by dose within these treatment groupings.

   Please include an overall summary of data that also includes data from Study 009 (alogliptin and pioglitazone combination therapy), which was submitted in NDA 22-271, as well as data from Studies 001 and 002, which will be submitted in the proposed NDA.

   The Subgroups Used in Data Presentations are summarized in Table 3.a. (page 309 of meeting package). Please also include data for subgroups of glomerular filtration rate, as estimated by the Cockcroft-Gault and MDRD equations, and data for subgroups of urinary albumin/creatinine ratio (if these data are available)

8. Does the FDA agree that the planned efficacy data presentation, as proposed in the briefing document, for Section 2.7.3 Summary of Clinical Efficacy of the NDA is appropriate and adequate to support the Agency's review of efficacy data?

   Division Response: Yes. It appears appropriate. For study 001, please perform the comparisons of FDC to components alone only when the primary analysis for the given FDC dose is significant in the primary analysis. Also, please include a dose response surface analysis as a supportive analysis. For Study 002, please compare the 12.5 mg alogliptin+30 mg pioglitazone to the 25 mg alogliptin alone group as an exploratory analysis.

9. Does the Agency concur with TGRD's proposal to submit similar electronic data sets and supporting documentation for NDA filing of SYR-322-4833?

   Division Response: Yes. It appears appropriate.

   However, we note that there is no unique patient identification variable in the submitted NDA 22-271 for alogliptin. We note that the patient identification variable in NDA 22-271 comprises <u>center + patient number</u> <u>but</u> the <u>study number</u> is a separate variable. We encourage the use of CDISC and the CDISC naming of a <u>unique subject identification</u> variable that includes <u>study number as well as center and patient number</u>. Please include such a unique subjection identification variable in the proposed NDA for both efficacy and safety data.

10. Does the Agency agree that similar format the organization of the patient profile will be acceptable for NDA filing of SYR-322-4833?

    Division Response: The patient profile information in NDA 22-271 for alogliptin comprises narratives and case report forms for deaths, other serious adverse events, and withdrawals from studies. In the preliminary review of the alogliptin NDA, we have noted potential cardiovascular and renal signals. Therefore, please also include similar patient profile information for all cardiovascular non-serious adverse events and for all serious and non-serious renal adverse events. Additional information may be requested pending further review of the alogliptin NDA.

Administrative/Regulatory

11. Are these proposed plans [regarding cross-referencing documents contained in the alogliptin NDA 22-271 and the pioglitazone NDA 21-073, and not submitting an independent proposal for a risk management plan] acceptable to the Agency?

    Division Response: Your proposal to cross-reference documents contained in the alogliptin and pioglitazone NDAs is acceptable.

    At this time in your drug development program, we are unable to determine all of the risk management efforts that may be needed for this fixed-dose combination, as new safety issues may be uncovered during NDA review that would require further risk management efforts beyond professional labeling and routine pharmacovigilance.

12. Does the Agency concur with this request [for a deferral from the requirement to conduct studies in the pediatric population]?

    Division Response: Your request is reasonable. However, a formal request with an accompanying rationale will need to be included in your NDA. A final decision cannot be made until we discuss this request with the Pediatric Review Committee (PeRC).

Additional FDA Comment

Please provide the number of patients included in this FDC NDA who will be exposed to both alogliptin and pioglitazone (by dose of each drug, and by study) for one year or longer. Include the number of patients who are enrolled in the open-label study from Studies 001, 002, and 009.

If you have any questions, contact Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 73193	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	SYR-322-4833(PIOGLITAZONE HCL)TABLETS

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/s/

MARY H PARKS
05/07/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 73,193

Takeda Global Research & Development Center, Inc.
Attention: Mary Jo Pritza, MPH, PharmD
Senior Manger, Regulatory Affairs
475 Half Day Road
Lincolnshire, IL 60069

Dear Ms. Pritza:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYR-322-4833 fixed-dose combination tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 8, 2006. The purpose of this pre-IND meeting was to discuss the development plan for your compound.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEETING DATE:	Wednesday February 8, 2006
APPLICATION:	P-IND 73,193 (pioglitazone HCl + SYR-322) fixed-dose combination tablets
TYPE OF MEETING:	Pre-IND
MEETING CHAIR:	Karen Mahoney, M.D., Acting Team Leader – Diabetes Division of Metabolism & Endocrinology Products (DMEP)
MEETING RECORDER:	Jena Weber, Project Manager

Division of Metabolism and Endocrinology Products (DMEP):

Karen Mahoney, M.D.	Acting Team Leader - Diabetes
Eddie Gabry, M.D.	Clinical Reviewer
Jena Weber, BS	Project Manager

Office of Clinical Pharmacology & Biopharmaceutics (OCPB):

Hae-Young Ahn, Ph.D.	Team Leader - Biopharmaceutics
Jim Wei, M.D., Ph.D.	Biopharmaceutics Reviewer

Office of Biometrics II, HFD-715

Todd Sahlroot, Ph.D.	Team Leader - Biometrics
Lee-Ping Pian, Ph.D.	Biometrics Reviewer

Takeda Global Research & Development Center, Inc.

Mary Jo Pritza, PharmD, MPH	Sr. Manager, Regulatory Affairs
Qais Mekki, M.D., Ph.D.	VP, Clinical Research
Aziz Karim, Ph.D.	VP, Phase 1, Clinical Research
Penny Fleck, MT	Program Manager
Craig Wilson, Ph.D.	Project Statistician
Christie Wong, MS	Program Manager, Regulatory Affairs

Meeting Purpose: To discuss the nonclinical and clinical data of each individual component intended to support the development program for SYR-322-4833, and the design of the proposed pivotal coadministration study, intended to support the development program for SYR-322-4833.

Objectives: Obtain concurrence on (1) the design of the pivotal coadministration study and data to support the development program for SYR-322-4833 and (2) the regulatory strategy to support the SYR-322-4833 fixed dose combination product.

Proposed Indication: Indicated as an adjunct to diet and exercise as a once-daily combination therapy for the treatment of type 2 diabetes mellitus to improve glycemic control (b) (4)

Nonclinical

A full complement of nonclinical evaluations of SYR-322 as a single agent, including acute and chronic toxicity, mutagenicity, reproductive toxicity, and carcinogencity studies, have been completed or are currently ongoing under IND 69,707. In the FDA memorandum of pre-meeting minutes for the End of Phase II meeting held on
November 28th, 2005, the Agency noted the current battery of nonclinical studies with a 3-month monkey study appear adequate to support NDA filing of SYR-322 for the proposed indication as a monotherapy and as a combination therapy with metformin, a sulfonylurea, a thiazolidinedione (TZD) or insulin.

Question: Because no substantial differences in safety profile are predicted between combination therapy with a TZD and fixed dose combination tablet with pioglitazone HCl, TGRD has no plan of additional nonclinical studies specialized for SYR-322-4833 fixed dose combination tablet. Does the Agency find this acceptable?
FDA Response: Yes.

Clinical

TGRD plans to open the SYR-322-4833 IND with a phase 3, double-blind, placebo-controlled, randomized, multicenter, 26-week coadministration study (01-05-TL-322OPI-001). This pivotal, factorial study is designed to evaluate the safety and efficacy of SYR-322 alone and in combination with pioglitazone in subjects with type 2 diabetes mellitus who have inadequate glycemic control on metformin monotherapy. SYR-322 doses of 12.5 or 25 mg together with pioglitazone doses of 15, 30, or 45 mg will be administered in this study. It is intended that this study will support the safety and efficacy of SYR-322 + pioglitazone combination therapy in patients with type 2 diabetes mellitus.
TGRD plans to develop the SYR-322-4833 fixed-dose combination product in 6 tablet strengths, containing the following amounts of SYR-322/pioglitazone: 12.5/15 mg, 25/15 mg, 12.5/30 mg, 25/30 mg, 12.5/45 mg, and 25/45 mg. The highest tablet strength (25/45 mg) will be evaluated in a pivotal bioequivalence study in which exposure of both SYR-322 and pioglitazone achieved after administration of SYR-322-4833 will be compared with that achieved after administration of the individual SYR-322 25 mg and pioglitazone 45 mg tablets.

TGRD plans to support the remaining SYR-322-4833 tablet strengths based on dose proportionality, assuming bioequivalence between the SYR-322-4833 25/45 mg tablets and the individual SYR-322 25 mg and pioglitazone 45 mg tablets. (b) (4) SYR-322-4833 tablets will be assessed in a (b) (4) crossover study (b) (4) In addition, a single dose, pharmacokinetic study to assess the effect of food on exposure of SYR-322-4833 when administered at the highest tablet strength (25/45 mg) will also be performed.
The clinical development of SYR-322-4833 will be further supported by studies being conducted as part of the single-agent clinical program for SYR-322 (IND 69,707). These studies include a phase 1 drug-drug interaction study with SYR-322 and pioglitazone, and a phase 3 study evaluating SYR-322 at doses of 12.5 and 25 mg in combination with pioglitazone in subjects with type 2 diabetes mellitus who have inadequate glycemic control on a thiazolidinedione with or without metformin or a sulfonylurea (Study SYR-322-TZD-009).

Assuming the safety and efficacy data are favorable, TGRD intends to submit the NDA for SYR-322-4833 concurrent with the Agency's review of the NDA for SYR-322 as a single agent.

Question 1

Does the Agency concur with TGRD's proposal for conducting a bioequivalence study and a food-effect study with the highest SYR-322-4833 tablet strength (25/45 mg) followed by a dose-proportionality study to support the bioavailability of the remaining tablet strengths?

FDA Response: 1. If the drug interactions study between pioglitazone and SYR-322 has not been conducted, a 4-way crossover BE study is recommended with the highest strengths (25 mg/45 mg):

- **In combination**
- **With two individual drugs**

For the lowest strength (12.5 mg/15 mg), a 2-way crossover BE study is recommended:

- **In combination**
- **With two individual drugs**

We can waive a BE study for the combinations using 30 mg of pioglitazone based on comparable dissolution profiles.

2. The proposed (b) (4) **study may not be needed.**

3. The proposed food study with the highest strength is acceptable.

4. The induction potential on P450 enzymes by SYR-322 should be addressed by either in vitro or in vivo studies. The sponsor indicated that they would address the induction potential.

Question 2

Does the Agency agree that the proposed NDA package for SYR-322-4833, consisting of (a) the factorial-design coadministration study, (b) the above-mentioned bioavailability studies, and (c) the studies conducted as part of the SYR-322 development program, would be sufficient to support the registration of the fixed-dose combination product for the proposed indication?

FDA Response: Provided that the clinical development program is modified according to the Division's response to questions 1 and 3, the above-mentioned studies will likely suffice for the NDA filing of SYR-322-4833. Depending on the quality of data submitted, SYR-322-4833 may be indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and SYR-322, or who do not have adequate glycemic control on pioglitazone alone or on SYR-322 alone.

SYR-322-4833 may also be indicated as an add-on to metformin in patients with type 2 diabetes already treated with metformin and who require additional glycemic control.

The proposed statistical analysis plan for the SYR-322-4833 phase 3 coadministration study (Study 01-05-TL-322OPI-001).

Question 3

Does the Agency agree that the methodology proposed for the primary and supportive analyses would be sufficient to support the registration of the fixed-dose combination product?

FDA Response: The Agency stated that the secondary (individual cell) comparisons on the primary endpoint should be considered primary and may be conducted at nominal significance levels. The sponsor expressed concern that in contrast to the proposed primary analysis comparing SYR-322 and pioglitazone combination therapy, and pioglitazone monotherapy (pooled across pioglitazone doses), the cell-to-cell comparisons may fail due to a lack of statistical power. FDA acknowledged that according to the sample size calculations, individual cells were powered at 90% to detect a treatment difference of 0.47% which the sponsor confirmed. Takeda commented that overall power (all comparisons being significant) was much lower than 90% due to the large number of comparisons and the relatively small treatment effect (0.3%) expected for some comparisons. FDA responded that both statistical and clinical judgment are essential with respect to assessing the efficacy of different dose combinations. For example, if all the comparisons were significant except for one comparison at p = .06, FDA would be comfortable with declaring efficacy particularly if the borderline p-value was not associated with the lowest doses.

- **FDA agreed that dose surface response methods (to better understand the response at different dose combinations) would be an adequate supportive analysis.**

- **Takeda requested a commitment that a statistical "trend" for comparisons of individual cells would constitute confirmation of efficacy. The Agency did not commit to this.**

- **The sponsor was asked to submit a complete protocol for FDA review and comment that reflected the meeting discussion.**

- **In summary, FDA did not disagree with the primary analysis but considers the secondary (cell-to-cell) analyses the most important part of the statistical review. These results will be carefully evaluated when assessing efficacy.**

Post-meeting comment

- **The sponsor's proposed analyses address the efficacy of SYR-322 only as add-on therapy to pioglitazone. The analyses do not address the fixed combination aspect of therapy in which the combination must be superior to each monotherapy arm. This point was not explicitly verbalized at the meeting, but it should be emphasized. Although pioglitazone has demonstrated efficacy in previous clinical trials, the efficacy of pioglitazone when used in a fixed combination with SYR-322 must be evaluated relative to SYR-322 monotherapy under the particular circumstances of this clinical trial.**

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/s/

Jena Weber
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