

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203414Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # **203414**

SUPPL # **n/a**

HFD # **n/a**

Trade Name **Kazano**

Generic Name **Alogliptin and metformin 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)(2)

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# **020357** **Glucophage (metformin hydrochloride) 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:

MET-302 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM

322-008 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR-322 when used in combination with metformin in subjects with T2DM

OPI-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

MET-101 - a phase 1, open-label, randomized, 2-cohort, 4-sequence, 4-period crossover, bioequivalence study in healthy subjects

MET-102 - a phase 1, open-label, randomized, 2-period crossover, food-effect study in healthy subjects

322-005 - a phase 1, randomized, open-label, 3-period, 6-sequence, crossover, drug-drug interaction study with metformin and alogliptin in healthy subjects

322-101 - a phase 1, open-label, multiple-dose, randomized, 2-period crossover, PK and PD study in healthy subjects

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: MET-302	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2: 322-008	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3: OPI-004	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4: MET-101	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5: MET-102	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6: 322-005	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #7: 322-101	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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: MET-302	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2: 322-008	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3: OPI-004	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4: MET-101	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5: MET-102	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6: 322-005	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #7: 322-101	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

MET-302 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with T2DM

322-008 – A multicenter, randomized, double blind, placebo controlled study to determine the efficacy and safety of SYR-322 when used in combination with metformin in subjects with T2DM

OPI-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

MET-101 - a phase 1, open-label, randomized, 2-cohort, 4-sequence, 4-period crossover, bioequivalence study in healthy subjects

MET-102 - a phase 1, open-label, randomized, 2-period crossover, food-effect study in healthy subjects

322-005 - a phase 1, randomized, open-label, 3-period, 6-sequence, crossover, drug-drug interaction study with metformin and alogliptin in healthy subjects

322-101 - a phase 1, open-label, multiple-dose, randomized, 2-period crossover, PK and PD study in healthy subjects

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: **MET-302** !
!
IND # **101628** YES ! NO
! Explain:

Investigation #2: **322-008** !
!
IND # **101628** YES ! NO
! Explain:

Investigation #3: **OPI-004** !
!
IND # **101628** YES ! NO
! Explain:

Investigation #4: **MET-101** !
!
IND # **101628** YES ! NO
! Explain:

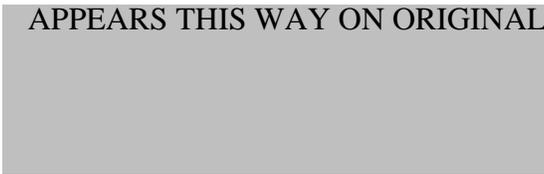
Investigation #5: **MET-102** !
!
IND # **101628** YES ! NO
! Explain:

Investigation #6: **322-005** !
!
IND # **101628** YES ! NO
! Explain:

Investigation #7: **322-101** !
!
IND # **101628** YES ! NO
! Explain:

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

APPEARS THIS WAY ON ORIGINAL



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 203-414, alogliptin/metformin 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.



Jennifer Dalton
Sr Director PDD Compound Support QA
Takeda Global Research and Development Center, Inc.

14 Nov 2011
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203414 BLA # N/A	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Kazano Established/Proper Name: alogliptin and metformin hydrochloride 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)
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Glucophage (metformin hydrochloride) tablets (NDA 020357)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This is a fixed dose combination with alogliptin and metformin</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain) N/A</p> <p><u>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.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is December 22, 2012 • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR N/A

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.

<p>❖ 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</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1, 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required </p> <p>Comments: Major Amendment submitted on 08/16/12, PDUFA goal date changed from 9/22/12 to 12/22/12</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) N/A</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) N/A</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # N/A and date exclusivity expires: N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # N/A and date exclusivity expires: N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # N/A and date exclusivity expires: N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # N/A and date exclusivity expires: N/A
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # N/A and date 10-year limitation expires: N/A
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire N/A
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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?

Yes No

(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)).

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?

Yes No

(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," 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	1-25-13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	1-25-13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	8-09-12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Package inserts for Janumet (sitagliptin/metformin; 10/18/2012) and Glucophage (metformin; 8/27/2008)

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide 1-25-13 <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	1-03-12 (final-agreed)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7-25-11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Medication Guide for Januvia (sitagliptin) and Actos (pioglitazone)
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	12-06-12
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	7-19-12; 4-17-12; 2-21-12 11-21-12; 7-19-12; 4-16-12
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 11-06-12; 1-14-13; 1-18-13 <input checked="" type="checkbox"/> DRISK 1-03-13 <input checked="" type="checkbox"/> DDMAC 1-18-13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 1-18-13 (DMPP)
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	3-23-12 (RPM filing review)
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 1-25-13 <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included 1-29-13
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC: 8-22-12 If PeRC review not necessary, explain: • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included 8-22-12 (PeRC minutes)

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 (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	IR:1-25-13; 1-25-13; 1-25-13; 1-23-13; 1-18-13; 1-14-13; 1-10-13; 1-8-13; 1-7-13; 1-4-13; 1-2-13; 12-20-12; 12-11-12; 11-14-12; 11-5-12; 9-26-12; 9-21-12; 8-28-12; 8-10-12; 6-29-12; 5-25-12; 5-16-12; 5-07-12; 2-2-12; 1-30-12; 1-13-12; 12-20-11; 11-29-11; 11-28-11 Memo to file: 11-9-12; 3-29-12; 2-3-12
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/> None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	No meeting
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	Written Response 4-5-11
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	No meeting
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	1-25-13
Division Director Summary Review (<i>indicate date for each review</i>)	1-24-13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1-24-13
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None See CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	1-21-13; 1-10-12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Usually within the Clinical reviews 1-21-13 page # 23
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	11-10-12 (OSE Liver review)

⁵ Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	Summaries: 8-2-12 Letters: 11-16-12; 9-13-12 Consult review: 1-14-13
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	7-17-12; 1-4-12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	7-27-12; 1-10-12
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	7-9-12
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	1-4-13 7-23-12; 1-11-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		12-21-12; 9-12-12; 8-7-12; 8-6-12; 7-27-12; 7-26-12; 3-29-12; 1-20-12; 1-10-12
❖ Microbiology Reviews		
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		none
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		7-26-12 page 154
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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 sites⁶)</i>		Date completed: 12-21-12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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.

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 PIs
Date: Friday, January 25, 2013 11:52:00 AM
Attachments: [Kazano- PI final.doc](#)
[Nesina-PI final.doc](#)
[Oseni-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 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

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
Deerfield, IL 60015
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M [REDACTED] (b) (6)

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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 we ask that 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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###

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

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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 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

Takeda Global Research & Development Center, Inc.
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T 224-554-1957
M (b) (6)

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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 we ask that 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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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.

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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 we ask that 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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###

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/s/

RICHARD E WHITEHEAD
01/25/2013

From: Whitehead, Richard
To: [Cosner, Sandra \(TGRD\) \(sandra.cosner@takeda.com\)](mailto:sandra.cosner@takeda.com)
Cc: [Barnes-Glait, Diane \(TGRD\) \(diane.barnes-glait@takeda.com\)](mailto: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](#)

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 we ask that 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

APPEARS THIS WAY ON ORIGINAL

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/s/

RICHARD E WHITEHEAD
01/18/2013

From: Whitehead, Richard
To: [Cosner, Sandra \(TGRD\) \(sandra.cosner@takeda.com\)](mailto:sandra.cosner@takeda.com); [Barnes-Glait, Diane \(TGRD\) \(diane.barnes-glait@takeda.com\)](mailto: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

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.

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sandra.cosner@takeda.com

www.tgrd.com

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/s/

RICHARD E WHITEHEAD
01/23/2013

From: Whitehead, Richard
To: [Cosner, Sandra \(TGRD\) \(sandra.cosner@takeda.com\)](mailto:sandra.cosner@takeda.com)
Cc: [Barnes-Glait, Diane \(TGRD\) \(diane.barnes-glait@takeda.com\)](mailto: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](#)

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;

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

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/s/

RICHARD E WHITEHEAD
01/14/2013

From: Whitehead, Richard
To: [Cosner, Sandra \(TGRD\) \(sandra.cosner@takeda.com\)](mailto:sandra.cosner@takeda.com)
Cc: [Barnes-Glait, Diane \(TGRD\) \(diane.barnes-glait@takeda.com\)](mailto:diane.barnes-glait@takeda.com)
Subject: NDA22271 and NDA203414: Revised Carton and Container Labeling
Date: Thursday, January 10, 2013 7:07:00 AM

Dear Sandy,

We have reviewed the revised carton and container labeling for Nesina (alogliptin) and Kazano (alogliptin and metformin) submitted on January 9, 2013 and the addition of the statement "Dispense with Medication Guide" is acceptable for both Nesina and Kazano. However, upon further evaluation of the carton and container labeling, we have the following recommendations:

Nesina:

- If the blister card packaging is not child-resistant, we recommend adding the statement "Enclosed Packages Are Not Child Resistant. Keep out of reach of children" to the professional sample blister card carton labeling, so that it is consistent with Oseni (alogliptin and pioglitazone).
- On the Principal Display Panel of the professional sample bottle carton labeling, add the statement "Contains 4 patient bottle samples of 7 tablets each," so that it is consistent with Oseni (alogliptin and pioglitazone).
- On the Principal Display Panel of the professional sample blister card carton labeling, add the statement "Contains 4 patient blister samples of 7 tablets each," so that it is consistent with Oseni (alogliptin and pioglitazone).

Kazano

- If the blister card packaging is not child-resistant, we recommend adding the statement "Package Not Child Resistant. Keep out of reach of children" to the professional sample blister card container label, so that it is consistent with Oseni (alogliptin and pioglitazone).
- If the blister card packaging is not child-resistant, we recommend adding the statement "Enclosed Packages Are Not Child Resistant. Keep out of reach of children" to the professional sample blister card carton labeling, so that it is consistent with Oseni (alogliptin and pioglitazone).

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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RICHARD E WHITEHEAD
01/10/2013

From: Whitehead, Richard
To: [Cosner, Sandra \(TGRD\) \(sandra.cosner@takeda.com\)](mailto: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)

Parameter (Criterion)	Number (%) of Subjects With ≥ 1 Marked Abnormal Result			
	Baseline		Post-Baseline	
	Placebo N=1466	Alogliptin N=1467	Placebo N=1372	Alogliptin N=1387
ALT ($>20 \times$ ULN)	0	0	0	0
ALT ($>10 \times$ ULN)	1 (0.1%)	2 (0.1%)	0	5 (0.4%)
ALT ($>8 \times$ ULN)	1 (0.1%)	2 (0.1%)	0	6 (0.4%)
ALT ($>5 \times$ ULN)	2 (0.1%)	5 (0.3%)	1 (0.1%)	10 (0.7%)
ALT ($>3 \times$ ULN)	13 (0.9%)	18 (1.2%)	5 (0.4%)	17 (1.2%)
$>3 \times$ ULN and total bilirubin >2.0 mg/dL	0	0	0	0
$>3 \times$ ULN and total bilirubin $>2 \times$ 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 $> 10 \times$ ULN in the 'during treatment' column but 5 patients in Table 7 w/ ALT $> 10 \times$ ULN in the post-baseline column. Please explain this discrepancy of one patient.”

Parameter	Number (%) of Subjects With ≥ 1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389
ALT $>3 \times$ ULN and total bilirubin $>2 \times$ ULN	0	0	1 (0.04)	1 (0.04)	0	1 (0.04)
ALT $>20 \times$ ULN	0	0	1 (0.04)	0	0	0
ALT $>10 \times$ ULN	1 (0.04)	2 (0.08)	2 (0.08)	4 (0.17)	0	1 (0.04)
ALT $>5 \times$ ULN	2 (0.08)	2 (0.08)	12 (0.51)	19 (0.80)	2 (0.08)	5 (0.21)
ALT $>3 \times$ 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

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)

Parameter	Number (%) of Subjects With ≥ 1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3 \times ULN and total bilirubin >2 \times ULN	0	0	0	0	0	0
ALT >20 \times ULN	0	0	0	0	0	0
ALT >10 \times ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5 \times ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3 \times 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

Takeda Global Research & Development Center, Inc.

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www.tgrd.com

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)

Parameter	Number (%) of Subjects With ≥ 1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3xULN and total bilirubin >2xULN	0	0	0	0	0	0
ALT >20xULN	0	0	0	0	0	0
ALT >10xULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5xULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3xULN	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 \(TGRD\) \(sandra.cosner@takeda.com\)](mailto: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.

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

Parameter	Number (%) of Subjects With ≥ 1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3xULN and total bilirubin >2xULN	0	0	0	0	0	0
ALT >20xULN	0	0	0	0	0	0
ALT >10xULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5xULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3xULN	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 \(TGRD\) \(sandra.cosner@takeda.com\)](mailto: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)

Parameter	Number (%) of Subjects With Markedly Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
	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)

Parameter	Number (%) of Subjects With ≥ 1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
	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: LAS 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 \(TGRD\) \(sandra.cosner@takeda.com\)](mailto:sandra.cosner@takeda.com)
Cc: [Barnes-Glait, Diane \(TGRD\) \(diane.barnes-glait@takeda.com\)](mailto: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](#)

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



NDA 203414

GENERAL ADVICE

Takeda Pharmaceuticals U.S.A. Inc.
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kazano (alogliptin and metformin hydrochloride) tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg.

We refer to your December 6, 2012, submission, containing revised carton and container labels for all strengths and package sizes. We also refer to our letter dated November 14, 2012, containing the requested revisions to the carton and container labels.

We have reviewed the referenced material and have the following comment:

[Redacted content] (b) (4)

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
12/11/2012



NDA 203414

GENERAL ADVICE

Takeda Pharmaceuticals, U.S.A., Inc.
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kazano (alogliptin and metformin) tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg.

We also refer to your August 7, 2012, submission, providing the container label, carton, and insert labeling for the proposed proprietary name, Kazano (Alogliptin and Metformin) Tablets.

We have reviewed the referenced material and have the following container label and carton labeling recommendations:

A. Comments Regarding Professional Sample Size

(b) (4)



B. Container Label

a. 12.5 mg/500 mg and 12.5 mg/1000 mg; All sizes

Although the established name is at least half the size of the proprietary name, the established name appears less prominent due to the use of different font. Thus, we request you revise the established name in accordance with 21 CFR 201.10 (g)(2), taking into account all factors, including typography, layout, contrast and other printing features.

b. 12.5 mg/500 mg strength; All sizes

The information in black-colored font (i.e., established name, dosage form, and strength) is difficult to read (b) (4)

(b) (4)
While revising the background color, ensure there is sufficient differentiation between the two strengths of the product.

c. 12.5 mg/500 mg strength; Professional blister card sample

(b) (4)
The black-colored writing is difficult to read (b) (4)
While revising the background color, ensure there is sufficient differentiation between the two strengths of the product.

C. **Carton Labeling**

a. 12.5 mg/500 mg and 12.5 mg/1000 mg; Professional Sample

Although the established name is at least half the size of the proprietary name, the established name appears less prominent due to the use of different font. Thus, we request you revise the established name in accordance with 21 CFR 201.10 (g)(2), taking into account all factors, including typography, layout, contrast and other printing features.

b. 12.5 mg/500 mg strengths; Professional Sample

(b) (4)
The black-colored writing is difficult to read (b) (4)
While revising the background color, ensure there is sufficient differentiation between the two strengths of the product.

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
11/14/2012

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

From: Whitehead, Richard
To: [Cosner, Sandra \(TGRD\) \(sandra.cosner@takeda.com\)](mailto: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 \(TGRD\) \(sandra.cosner@takeda.com\)](mailto:sandra.cosner@takeda.com)
Subject: NDA22271 and NDA 203414 Study SYR-322_309 Reviewer Comments
Date: Friday, September 21, 2012 9:33:00 AM

NDA 22271 alogliptin
NDA 203414 alogliptin/metformin

Sandy,

We have the following preliminary statistical review comments, based on the NDA22271 and NDA203414 synopsis of Study SYR-322_309:

(b) (4)



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



NDA 203414

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Takeda Pharmaceuticals USA, Inc.
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) dated November 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin/metformin fixed-dose combination (12.5 mg/500 mg, 12.5 mg/ 1000 mg) tablets.

On August 16, 2012, we received your August 16, 2012, unsolicited major amendment to this application. 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 **December 22, 2012**.

In addition, in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012,” the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our filing communication letter dated February 2, 2012, no longer applies and no new timeline will be provided.

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

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RICHARD E WHITEHEAD
08/28/2012

**PeRC PREA Subcommittee Meeting Minutes
August 22, 2012**

PeRC Members Attending:

Peter Starke
Dianne Murphy
Rosemary Addy
Patricia Dinndorf
Gregory Reaman
Shrikant Pagay
Andrew Mosholder
William Rodriguez
Lily Mulugeta
George Greeley
Kim Dettelbach
Courtney Suggs
Susan McCune
Coleen LoCicero
Karen Davis-Bruno
Bethany Baer

Guests Attending:

Jeannine Best (PMHS)	Alyson Karesh (PMHS)
Donna Snyder (PMHS)	Jeanine Best (PMHS)
Denise Pica-Branco (PMHS)	Amy Taylor (PMHS)
Nichella Simms (PMHS)	Renan Bonnel (OPT)
Dionna Green (OCP)	Michelle Roth-Cline (OPT)
Jean Temeck (OPT)	Maura O'Leary (CBER)
Erica Radden (PMHS)	Gerald Wharton (OPT)
Mildred Wright (PMHS)	Jeremiah Momper (OCP)
Jina Lee (OCP)	Stacy Barley (DGIEP)
Rich Whitehead (DMEP)	Sue-Chih Lee (OCP)
Dominic Chiapperino (DAAAP)	David Lee (OCP)
Ellen Fields (DAAAP)	Yun Xu (OCP)
Ruyi He (DAAAP)	Jean-Marie Guettier (DMEP)
Ray Chiang (DMEP)	Mary Parks (DMEP)

Agenda

10:00	BLA 125276/S-049	Actemra (tocilizumab) Partial Waiver/Deferral/Plan
10:30	(b) (4)	(b) (4)
11:00	(b) (4)	(b) (4)

Actemra Partial Waiver/Deferral/Plan

- BLA 125276/049, Actemra (tocilizumab), oral solution was studied for the relief of moderate to severe acute pain in patients 18 years of age or older
- The application was submitted on December 15, 2011, and has a PDUFA date of October 15, 2012.
- This application triggers PREA as a new active ingredient.

Waiving for those patients in polyarticular patients less than two year for as there are too few infants to conduct the study.

Deferral – study has already been submitted. (b) (4)

[Redacted]

[Redacted]

[Large Redacted Area]

(b) (4)



From: Hai, Mehreen
To: ["Barnes-Glait, Diane \(TGRD\)"](#)
Cc: [Whitehead, Richard](#)
Subject: RE: Update
Date: Friday, August 10, 2012 4:28:00 PM

Thank you, Diane.

One last thing I need to inform you of, although it will be obvious to you, is that we will not be sending you the proposed labeling and the PMRs right now, as we originally stated we would do by August 4, 2011 in our filing letter for this product.

Also, if you could email the pediatric plan dates to Rich, and then follow up with an official submission at your convenience, that would be great.

Thank you once again!

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: Barnes-Glait, Diane (TGRD) [<mailto:diane.barnes-glait@takeda.com>]
Sent: Friday, August 10, 2012 4:18 PM
To: Hai, Mehreen
Cc: Whitehead, Richard
Subject: RE: Update

Dear Mehreen,

Yes, I will update the pediatric plans with complete dates. I will try to get that done as soon as possible next week. We will also be submitting the major amendment next week as soon as the publishing is finalized.

I want to thank you for all your support on this project – it has truly been a pleasure working with you. I wish you all the best as you move into your new role. I look forward to working with Rich in the future.

Best regards,
Diane M. Barnes-Glait, M.S.
Manager, Regulatory Affairs
Regulatory Affairs Strategy

Takeda Global Research and Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015

224 554-2760 (phone)
(b) (6) (mobile)
224 554-7870 (fax)
diane.barnes@tgrd.com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, August 10, 2012 12:53 PM
To: Barnes-Glait, Diane (TGRD)
Cc: Whitehead, Richard
Subject: RE: Update

Hello Diane,

I did have one last request for you: can you submit an update to your pediatric plan that incorporates the complete milestone dates for the pediatric studies - i.e. month/day/year, not just month/year. And if you could do this in the next few days, that would be great.

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

From: Hai, Mehreen
Sent: Friday, August 10, 2012 12:34 PM
To: 'Barnes-Glait, Diane (TGRD)'
Cc: Whitehead, Richard
Subject: Update

Hello Diane,

I wanted to inform you that effective immediately, the alogliptin-metformin IND 101628 and NDA 203414 are being transferred to another project manager in our group, Rich Whitehead (cc'ed here). Rich is going to take over from me for all pending items on these applications. I am moving into different responsibilities in our division, but I will be working closely with Rich to familiarize him with these applications. If any question arises regarding their regulatory history, I will be fully available to answer any questions.

Thank you, and please let me know (and Rich) know if you have any questions.
It's been a pleasure working with you!

Rich's contact info:

Richard Whitehead
Regulatory Project Manager
(301) 796-4945

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
08/10/2012



NDA 203414

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

Attention: Diane M. Barnes-Glait, M.S.
Manager, Regulatory Affairs

Dear Ms. Barnes-Glait:

Please refer to your Investigational New Drug Application (IND) dated November 22, 2011, received November 22, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Metformin HCl Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg.

We also refer to your April 23, 2012, correspondence, received April 23, 2012, requesting review of your proposed proprietary name, Kazano. We have completed our review of the proposed proprietary name, Kazano and have concluded that it is acceptable.

The proposed proprietary name, Kazano, 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. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If **any** of the proposed product characteristics as stated in your April 23, 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 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/

IRENE Z CHAN on behalf of CAROL A HOLQUIST
07/20/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Friday, June 29, 2012 2:30 PM
To: 'diane.barnes-glait@takeda.com'
Cc: Hai, Mehreen
Subject: Information Request for NDA 203414

Dear Diane,

We have a CMC information request for you for NDA 203414. Please provide your response as an amendment to the NDA.

Your executed batch record information for Lot Z666406 appears to be missing information on alogliptin (b) (4). Please provide a copy of the missing batch record for alogliptin (b) (4).

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
06/29/2012

From: [Hai, Mehreen](#)
To: ["Barnes-Glait, Diane \(TGRD\)"](#)
Subject: RE: Info request for NDA 203414
Date: Friday, May 25, 2012 9:48:00 AM

Hi Diane,
Thanks for letting me know, and yes, it's fine to cross-reference all three INDs.

We have another information request for you, as follows:

In Section 12.3.1.3.1 of Interim Clinical Study Report 305, you state, "At the time of the interim data cut, reason for discontinuation from the study data and adverse event data were not 100% reconcilable. Therefore the number of subjects listed as discontinuing from the study due to an adverse event in Table 15.1.1 does not match the number of subjects who permanently discontinued study drug as presented in Table 15.3.2.1". With regards to this information, please clarify the following:

- Is Table 15.3.1.5 a summary of Table 15.3.2.1?

- Table 15.3.2.1 and Table 15.1.1 list 52 and 48 subjects discontinued in the A12.5+M group (respectively) and 62 and 64 subjects discontinued in the A25+M group (respectively). Please explain why the number of subjects listed in Table 15.1.1 who discontinued due to an adverse event for each treatment group is different from the number of subjects in Table 15.3.2.1. As part of this explanation, please submit a summary table (which includes subject identification numbers) of discontinuations for each of these tables by treatment group, SOC, and preferred term. Please also submit a list (including patient identification number, treatment group, SOC, and preferred term) of the non-reconcilable cases. Please include narratives for these nonreconcilable cases.

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: Barnes-Glait, Diane (TGRD) [mailto:diane.barnes-glait@takeda.com]
Sent: Friday, May 25, 2012 9:26 AM
To: Hai, Mehreen
Subject: RE: Info request for NDA 203414

Hi Mehreen,

We are submitting our response to this information request today. The information request asked that we also cross-reference the alo-mono and alo-met INDs with our submission. In addition to those two INDs, we are also planning to cross-reference the alo-pio IND to maintain consistency in

the information provided to each of the INDs. Please let me know if you have any concerns in our cross-referencing all 3 INDs.

Best regards,
Diane

Diane M. Barnes-Glait, M.S.
Manager, Regulatory Affairs
Takeda Global Research and Development, Inc.
(224) 554-2760 (phone)
(224) 554-7870 (fax)
diane.barnes@tgrd.com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Thursday, May 17, 2012 3:36 PM
To: Barnes-Glait, Diane (TGRD)
Subject: Info request for NDA 203414

Hello Diane,
Please find attached an information request letter for NDA 203414 that we issued yesterday.
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

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
05/25/2012



NDA 203414

INFORMATION REQUEST

Takeda Global Research and Development Center, Inc.
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) dated and received November 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for alogliptin and metformin hydrochloride fixed-dose combination (FDC) tablets (12.5 mg/500 mg, 12.5 mg/1000 mg).

In the clinical report for Study SYR-322MET_302, you identified 13 subjects who enrolled at two or more study sites, and ten subjects who enrolled both in Study 302 and in ongoing Study SYR-322_305. This finding was reported in Part 10.2 of the study report and described further in Appendix 16.2.4.5. We understand that these replicate enrollments were identified by Project Management (b) (4) by comparing demographic data of all enrolled subjects in Study 302. We appreciate your diligence in identifying this situation, addressing it, and documenting it in the study report.

We concur with the determinations you made concerning the status of each replicate enrollment in the full analysis set, the per protocol set and the safety set as documented in Appendix 16.2.4.5. However, this occurrence of replicate enrollments across studies 302 and 305 raises the possibility that there may be replicate enrollments in the cardiovascular outcomes study, Study SYR322_402. We believe that it is particularly important in Study 402 to establish the actual exposure to alogliptin and comparator drugs for each subject, and to attribute all cardiovascular outcomes comprehensively to each subject. Therefore, we have the following requests:

1. Please search the database of cardiovascular trial SYR-322_402 for subjects who either enrolled at multiple sites or who have also participated in any other alogliptin studies. Because SYR-322_402 is actively enrolling, repeat the search for replicate subjects after enrollment is complete. Identify and document any identified subjects in Study 402 as you have done for Study 302.
2. If any replicate enrollments are identified in Study 402, we would like to discuss their disposition with you before you unblind the database.

Please submit the requested information to the alogliptin-metformin FDC NDA, and include by cross-reference to the INDs for alogliptin and the alogliptin-metformin FDC. Please also include this information in the future resubmissions for the alogliptin and alogliptin-pioglitazone FDC NDAs.

If you have any questions, please contact 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 & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
05/16/2012



NDA 203414

INFORMATION REQUEST

Takeda Global Research and Development Center, Inc.
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Metformin Hydrochloride fixed-dose combination.

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 Product

- 1) Provide the size and operating capacity (b) (4)
[Redacted]
- 2) Results from the Pharmaceutical Development studies for the drug product Container /Closure systems indicated (b) (4)
[Redacted]
- 3) Note, that the Agency does not support the use of the term (b) (4)
[Redacted]

- [REDACTED] (b) (4)
- 4) [REDACTED] (b) (4)
Revise the proven acceptable ranges for operating process parameters including the key process parameters to a justifiable range [REDACTED] (b) (4)
- 5) Your manufacturing process description is inadequate with respect to information on target operating ranges or set point for operating parameters and does not provide a complete description of the commercial scale drug product manufacturing process and in-process controls. Adequate information should be provided to describe all the manufacturing steps and in-process controls. Thus, In accordance with 21CFR 314.50(d)(ii)(c), either provide a master batch record to any section of module 3, with a reference/link to the master batch record in the process description (section P.3.3) OR provide a process description to section P.3.3 that is comparably detailed to the master batch record. In addition, notification of all changes beyond the ranges provided for in the submission, including changes to non critical process parameters, should be communicated to the Agency in accordance with 21 CFR 314.70.
- 6) Include appropriate in-process controls [REDACTED] (b) (4)
- 7) To facilitate a thorough evaluation of your proposed design space, if available, provide a tabular summary of the DOE studies (e.g. inputs, outputs for all runs) associated with full scale optimization studies (Section 3.2.P.2.3).
- 8) To support your proposal of using disintegration as a surrogate for dissolution, provide data supporting the discriminating capability of disintegration testing. In general, the testing conducted to demonstrate the discriminating ability of disintegration testing /acceptance criterion should compare the disintegration of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant significant manufacturing variables [REDACTED] (b) (4)
- [REDACTED] In addition, if available, submit data showing the capability of disintegration testing to reject batches that are not bioequivalent.
- 9) Submit disintegration and dissolution profiles of drug product batches tested on pivotal Phase 3 clinical trials and bioequivalence study (ies), and provide the ranges of key formulation and process parameters [REDACTED] (b) (4) used in the manufacture of these batches.
- 10) Explain why the detection wavelength for the dissolution of both alogliptin and metformin HCl is set [REDACTED] (b) (4) when the UV spectrum of metformin HCl, depicted in Figures 5 & 6 in

the section on Identification by UV Absorption Spectrum, does not show any significant absorption for metformin HCl at this wave length.

- 11) Provide a proposed specification (analytical method and acceptance criteria) (b) (4) in order to qualify this material as a current and future Reference Standard for the Assay and Content Uniformity of your alogliptin/metformin HCl tablets. At a minimum, the specification should include acceptance criteria for Appearance, Identification and Assay. You should also indicate how often such a standard would be requalified.
- 12) Provide Identity Tests which uniquely identify the chemical composition of your packaging components, as for example, an IR spectrum that conforms to an appropriate reference of the material under consideration.
- 13) Provide a specification (b) (4) for all of your packaging components.
- 14) You indicated (b) (4) Correct this citation (b) (4) if this is appropriate.
- 15) Provide a drawing which shows the dimensions of your blister packages.
- 16) Establish a Leak test with appropriate requirements as an in-process control for your blister packages.
- 17) Provide a table outlining your (b) (4) plan for the post-approval lots of drug product that will be placed on stability.

If you have any questions, call Khushboo Sharma, Regulatory Project Manager, at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Division Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ERIC P DUFFY
05/07/2012



NDA 203414

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

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

Attention: Diane M. Barnes-Glait, M.S.
Manager, Regulatory Affairs

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) dated November 22, 2011, received November 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Metformin HCl Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg.

We also refer to your January 18, 2012, correspondence, received January 18, 2012, 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 unacceptable for the following reasons:

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill, covering the majority of the lower half of the page.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

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

¹ *Question-ERR Prescribing Combination Products*. Accessed 2-April-2012. www.med-errs.com/Question/Resulterr0408.asp.

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/s/

CAROL A HOLQUIST
04/17/2012



NDA 203414

**PROPRIETARY NAME REQUEST
WITHDRAWN**

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

Attention: Diane M. Barnes-Glait, M.S.
Manager, Regulatory Affairs

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) dated November 22, 2011, received November 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alogliptin and Metformin HCl Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg.

We also refer to the January 12, 2012, teleconference with the Agency to discuss your request for review for the proprietary names [REDACTED] (b) (4) as well as the alternate name [REDACTED] (b) (4)

We acknowledge receipt of your January 16, 2012, correspondence, received on January 17, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name [REDACTED] (b) (4) as well as the alternate [REDACTED] (b) (4). This proposed proprietary name request, as well as the alternate, is considered withdrawn as of January 17, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, 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
02/21/2012



NDA 203414

FILING COMMUNICATION

Takeda Global Research and Development Center, Inc
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

Please refer to your New Drug Application (NDA) dated and received November 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for alogliptin and metformin hydrochloride fixed-dose combination tablets (12.5 mg/500 mg, 12.5 mg/1000 mg).

We also refer to your amendment dated November 28, 2011.

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 **September 22, 2012**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 4, 2012.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

In your pending NDA for alogliptin (022271), you are seeking approval of alogliptin 25 mg daily for the treatment of type 2 diabetes in patients with normal renal function. (b) (4)



We are providing the above 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, expanded upon, or modified as we review the application.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Amundson Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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(s) 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 request, we will notify you of our decision regarding the partial waiver and/or the partial deferral requests.

If you have any questions, please contact 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 & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
02/02/2012

From: [Hai, Mehreen](#)
To: ["Barnes-Glait, Diane \(TGRD\)"](#)
Subject: Information request for NDA 203414
Date: Monday, January 30, 2012 4:18:00 PM

Hi Diane,
We have the following information request for NDA 203414 (alogliptin-metformin FDC):

Please submit the contact information (telephone and fax number, e-mail address) for the following investigators:

Bandgar Tushar Ramkrishna, MD, DM (Site 5254)
Michael Szczesny, MD (Site 5301)

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
01/30/2012

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

From: [Hai, Mehreen](#)
To: ["Cosner, Sandra \(TGRD\)"](#)
Subject: Info request for alogliptin NDAs
Date: Tuesday, December 20, 2011 2:38:00 PM

Hi Sandy,
We have the following information request for the NDAs for alogliptin (22271) and alogliptin-metformin (203414):

In the pediatric population, you should evaluate the efficacy and safety of alogliptin as monotherapy and in combination with metformin. You can either conduct a single phase 3 efficacy and safety trial that has two strata (a monotherapy stratum and an add-on to metformin stratum) or you can conduct two separate trials (a monotherapy trial and a separate add-on to metformin trial). In addition, while your proposed primary efficacy endpoint at 6 months is acceptable, there should be a controlled extension period so that the total treatment period is 1 year for your phase 3 pediatric trial(s). These requests are consistent with what we have expected with other recently approved treatments for type 2 diabetes. Submit a revised proposal to us for your pediatric phase 3 program within 1 month.

Please also submit an updated pediatric plan for alogliptin/metformin FDC after you revise the alogliptin pediatric plan. This updated plan should clarify how the revised pediatric phase 3 program for the alogliptin NDA will satisfy PREA for the alo/met NDA.

Thanks, and 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***

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/s/

MEHREEN HAI
12/20/2011



NDA 203414

NDA ACKNOWLEDGMENT

Takeda Global Research and Development Center, Inc
Attention: Diane Barnes-Glait
Manager, Regulatory Strategy
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Barnes-Glait:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Alogliptin and Metformin Hydrochloride fixed-dose combination tablets (12.5 mg/500 mg, 12.5 mg/1000 mg)

Date of Application: November 22, 2011

Date of Receipt: November 22, 2011

Our Reference Number: NDA 203414

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 **January 21, 2012**, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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.

You are also 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).

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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

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/s/

MEHREEN HAI
11/29/2011

From: [Hai, Mehreen](#)
To: ["Barnes-Glait, Diane \(TGRD\)";](#)
Subject: NDA 203414
Date: Monday, November 28, 2011 3:35:36 PM

Hi Diane,
I will shortly be sending you an acknowledgement letter for NDA 203414, but in the meantime we have the following information request:

Please submit a revised Form 356h to include the Establishment Information. The current form says "See attachment" but there is no attachment. Please include ALL manufacturing and testing sites of the commercial drug substance and drug product in the information, including the sites that are in the referenced NDAs and DMFs, and the contact for each site.

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
11/28/2011



IND 101628

**MEETING REQUEST -
Written Responses**

Takeda Global Research & Development Center, Inc.
Attention: Sangeeta Gupte, Ph.D.
Manager, Regulatory Affairs Strategy
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-322MET (alogliptin plus metformin HCL fixed-dose combination) tablets.

We also refer to your correspondence dated December 9, 2010, requesting a Pre-NDA meeting to discuss the format and content of the planned new drug application (NDA) for SYR-322MET. We also refer to our letter dated December 28, 2010, notifying you that we would provide a written response to the questions in your meeting package within 75 days after receiving your background materials. The meeting package was received on January 26, 2011. We also refer to our email dated February 1, 2011, notifying you that we consider your meeting package as a type C meeting package.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

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:
Written Responses

Your questions are repeated below, followed by our response in **bold** print.

1. The phase 3 studies examined separate and unique patient populations; therefore each study will be presented separately within Module 2.7.4 Clinical Summary of Safety of the NDA, and no integration or pooling of the datasets will be performed for discussion of safety. Does the Agency agree with this approach?

FDA Response: We agree with your plan to present Phase 1 studies MET-101, MET-102, 322-005, 322-101 and Phase 3 studies MET-302, 322-008, and OPI-004 separately and without integration or pooling for a safety analysis, due to differences in treatment populations and durations.

2. Does the Agency agree that these additional tables along with the standard individual study level safety summaries (eg, AE, laboratory, and vital sign summaries) are appropriate and adequate to support the Agency's review of the safety data?

FDA Response: We agree with the proposed study-specific, safety tables to summarize special interest adverse events, with the following exceptions:

- **Please analyze and provide narratives for major adverse cardiovascular events (MACE) in the Phase 3 studies.**
- **Please provide a textual analysis of the numeric tables.**

Please confirm that you plan to submit SAS transport datasets for the proposed analyses.

3. Does the Agency agree that a 120-day Safety Update is not applicable for this NDA?

FDA Response: No, we do not agree. The 120-day safety update should include the results from ongoing trials of alogliptin under other INDs (e.g., IND 069707 for alogliptin and IND 073193 for alogliptin/pioglitazone), post-marketing experience with alogliptin in other countries, results from animal toxicity studies and safety issues published in the literature.

4. Does the Agency agree with TGRD's plan to provide the complete study reports for non-IND studies in the NDA and not summarize the data from these studies within the NDA?

FDA Response: We concur with your proposal to provide complete study reports, including the synopses for the two Phase 3, non-IND (Japanese) studies that were conducted, to evaluate the safety and efficacy of alogliptin in combination with metformin and to not summarize the data from these studies within the NDA.

5. Does the Agency agree with TGRD's plan to cross-reference CMC, nonclinical, and clinical documents submitted to NDA 22-271 and 22-426?

FDA Response:

CMC:

Your plan to cross-reference the drug substance information for alogliptin from the alogliptin NDA 022271 Modules 2.3.S and 3.2.S is acceptable. Clearly indicate in the new NDA which information is being referenced. We remind you to submit the complete list of all manufacturing and testing facilities of the commercial drug substances and drug product in Form 356h of the new NDA with the statement that all facilities are ready for GMP inspection.

Non-Clinical and Clinical:

Your plan to cross-reference non-clinical and clinical documents from NDA 022271 and NDA 022426 is acceptable. Please include electronic hyperlinks to any cross-referenced data. We also request that you include summaries and discussion relevant to combination alogliptin plus metformin (non-clinical and clinical) and complete study reports of any studies not previously submitted in the alogliptin NDAs.

Please consider the following general guidelines when preparing your submission:

- Final study reports of the non-clinical studies are required at the time of NDA submission. Draft reports would not be acceptable.
- Histopathology data should include individual animal reports as well as tabulated data that includes incidence and severity scores.
- Include a table that specifies the drug batches used in non-clinical and clinical studies, including links to impurity profiles.

General information regarding cross-referencing:

Options for cross-referencing information submitted to another application would be to either place a "linked" cross reference document under module 1.4.4 (cross reference to other applications), or to use cross application links. For information required in module 1.4.4., please refer to page 5 of the eCTD Specifications located at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf>

If you do decide to use cross-application links, we recommend that you also provide the list of referenced documents under module 1.4.4., in case the links don't work, and then include the referenced leaf in the XML backbone. We also recommend that the leaf titles indicate the cross-reference and application number (e.g. Cross Ref to 123456). The cross-reference information in the leaf titles allows the reviewer to know that the document resides in another application and which application is being referenced.

In order to use cross-application links, all referenced applications should be in eCTD format and should all reside on the same server. The applications need to include the appropriate prefix in the href links (ind, nda, mf, or anda).

Prior to using cross application linking in an application, we recommend that you submit a sample to ensure that you are able to successfully use cross-application links. To submit an eCTD sample to test cross application linking, please refer to the Sample Process web page located at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

6. Pursuant to 21 Code of Federal Regulation (CFR) 314.55 (b)(1), TGRD is requesting a deferral from the requirement to conduct studies evaluating the SYR-322MET FDC product in the to characterize SYR-322MET more fully in the adult population prior to conducting studies in pediatric subjects. Does the Agency concur with this request for a deferral?

FDA Response: A decision regarding the waiver or deferral of pediatric studies under the Pediatric Research Equity Act (PREA) cannot be made until the NDA for alogliptin and metformin fixed-dose combination has been submitted and discussed with the Pediatric Review Committee (PeRC). However, at this time, we anticipate that pediatric studies will be waived in subjects 0-9 years and deferred in subjects 10-16 (inclusive) years.

7. TGRD plans to provide financial disclosure and certification for all “covered” studies as defined in 21 CFR § 54.2(e). This would include the phase 3 studies MET-302, 322-008, and OPI-004. Financial disclosure and certifications will not be included for phase 1 studies. Does the Agency agree with this plan for financial disclosure?

FDA Response: We agree with your plan to provide financial disclosure and certification information for Phase 3 studies and not for Phase 1 studies, provided that the Phase 1 studies did not involve a single investigator making a significant contribution to the demonstration of safety or the efficacy determination, as defined in 21 CFR 54.2(e).

Additional Clinical Pharmacology comments:

- Confirm that your bioequivalence study, SYR-322MET_101, evaluated the final, to-be-marketed fixed-dose combination formulation.
- Confirm that you have used the US-approved metformin products in your bioequivalence study and the Phase 3 studies.
- Plan to submit SAS transport datasets from the bioequivalence study and other relevant Phase 1 studies.

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

/s/

MARY H PARKS
04/05/2011