

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203414Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

Application Information		
NDA # <b>203414</b>	NDA Supplement #: S- <b>N/A</b>	Efficacy Supplement Type SE- <b>N/A</b>
Proprietary Name: <b>Kazano (pending review)</b>		
Established/Proper Name: <b>Alogliptin/Metformin Hydrochloride Fixed-Dose Combination</b>		
Dosage Form: <b>Tablets</b>		
Strengths: <b>12.5 mg/500 mg and 12.5 mg/1000 mg</b>		
Applicant: <b>Takeda Global Research and Development Center, Inc</b>		
Date of Receipt: <b>November 22, 2011</b>		
PDUFA Goal Date: <b>September 22, 2012</b>	Action Goal Date (if different): <b>January 25, 2013</b>	
Proposed Indication(s): <b>Treatment of Type 2 Diabetes Mellitus</b>		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
<b>Glucophage (metformin hydrochloride) tablets (NDA 020357)</b>	<b>Safety and efficacy data throughout US Prescribing Information</b>

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**BA/BE studies for Glucophage**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
<b>Glucophage (metformin hydrochloride)</b>	<b>NDA 020357</b>	<b>Y</b>

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: **N/A**

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process: **N/A**

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph: **N/A**

d) Discontinued from marketing?

YES  NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing: **N/A**

i) Were the products discontinued for reasons related to safety or effectiveness? **N/A**

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

**This application provides for a new fixed-dose combination of alogliptin and metformin hydrochloride, for the treatment of type 2 diabetes.**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If “**NO**” to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? N/A

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A

YES  NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): N/A

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? N/A

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): N/A

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **None**

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s): **N/A**

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): **N/A**

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): **N/A**

Expiry date(s): **N/A**

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): **N/A**

Method(s) of Use/Code(s): **N/A**

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): **N/A**

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): **N/A**

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RICHARD E WHITEHEAD  
01/25/2013

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 022271 Nesina (alogliptin)  
Product Name: 203414 Kazano (alogliptin and metformin hydrochloride)

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PMR/PMC Description: Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin compared to placebo when added to metformin for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10 to 17 years (inclusive). At least 30% of randomized subjects will be 10-14 years of age, and at least 1/3 and not more than 2/3 of subjects in both age subsets (10-14 years and 15-17 years) will be female.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/31/2015</u>
	Study/Trial Completion:	<u>07/31/2019</u>
	Final Report Submission:	<u>01/31/2020</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Alogliptin is ready for approval for use in adults; however, the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric study required under PREA to assess the efficacy and safety of alogliptin compared with placebo when added on to metformin for the treatment of T2DM in pediatric patients ages 10 to 17 years (inclusive).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin compared to placebo when added on to metformin in pediatric patients 10 through 17 years (inclusive) with T2DM. At least 30% of randomized subjects will be 10-14 years of age. At least 1/3 and not more than 2/3 of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Subpopulation: Pediatric patients ages 10 to 17 years (inclusive) with T2DM

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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 022271 Nesina (alogliptin)  
Product Name: 022426 Oseni (alogliptin and pioglitazone)  
203414 Kazano (alogliptin and metformin hydrochloride)

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PMR/PMC Description: An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with alogliptin – both foreign and domestic cases. Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and 10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

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PMR/PMC Schedule Milestones:

Final Protocol Submission:	10/31/2013
Interim Report Submissions:	03/31/2014
	03/31/2015
	03/31/2016
	03/31/2017
	03/31/2018
	03/31/2019
	03/31/2020
	03/31/2021
	03/31/2022
Study/Trial Completion:	01/31/2023
Final Report Submission:	09/30/2023
Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Review of clinical trial and Japanese postmarketing data has revealed cases of hepatotoxicity for which no satisfactory or convincing diagnosis, other than the use of alogliptin, was found. Given the low incidence of this safety signal, enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of this drug.

A serious risk of pancreatitis is a potential safety concern related to the DPP4 inhibitor class of drugs, including alogliptin. Enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of the drug.

A serious risk of hypersensitivity is a potential safety concern related to the DPP4 inhibitor class of drugs, including alogliptin. This risk may be enhanced by concomitant administration of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of the drug and concomitant medication administration.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the enhanced pharmacovigilance study is to gather additional data on known and potential serious risks related to the long-term use of alogliptin.

The program will include:

a) Active query of reporters to obtain additional clinical information related to reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions. The sponsor should actively query reporters for the following information:

- 1) For reports of serious hepatic abnormalities the sponsor should actively query reporters for liver-related laboratory (including viral serology), imaging and pathology results, duration of alogliptin exposure, and other risk factors for hepatic abnormalities.
- 2) For reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis the sponsor should actively query reporters for related laboratory values (including triglyceride, lipase, and amylase values), confirmatory imaging and pathology results, duration of alogliptin exposure, and other risk factors for pancreatitis.
- 3) For reports of severe hypersensitivity reactions the sponsor should actively query reporters for concomitant medication use (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers), biopsy results, duration of alogliptin exposure, and other risk factors for hypersensitivity reactions.

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

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal and hemorrhagic/necrotizing pancreatitis, and 10 years from the date of approval for reports of hepatic abnormalities and severe hypersensitivity reactions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
  
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Enhanced pharmacovigilance program for reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis (HNP), and severe hypersensitivity reactions in patients treated with alogliptin for a period of 5 years from the date of approval for fatal pancreatitis and HNP and 10 years from the date of approval for hepatic abnormalities and severe hypersensitivity reactions to collect data that will be analyzed to better define these risks. The enhanced pharmacovigilance program includes the following:

- a) Active query of reporters to obtain additional clinical information related to reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions.
- b) Expedited reporting to FDA of all initial and follow-up reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis with a serious outcome, and severe hypersensitivity reactions.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Enhanced pharmacovigilance
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMY G EGAN  
01/24/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
Division of Professional Drug Promotion (DPDP)  
Division of Consumer Drug Promotion (DCDP)**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** January 18, 2013

**To:** Rich Whitehead, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Samuel M. Skariah, Regulatory Review Officer, DPDP  
Kendra Y. Jones, Regulatory Review Officer, DCDP

**Subject: OPDP Labeling Review**  
NDA #022271 NESINA (alogliptin) tablets  
#022426 OSENI (alogliptin and pioglitazone) tablets  
#203414 KAZANO (alogliptin and metformin HCl) tablets

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OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (Med Guide), and carton/container labeling for the products listed above consulted from DMEP to OPDP on January 7, 2008, October 1, 2008, August 3, 2011, December 7, 2011, and September 17, 2012. OPDP has reviewed the proposed version of these documents accessed from the eRoom on January 16, 2013 and offers the following comments.

Comments regarding the PI and Med Guide are provided in the marked versions below. OPDP has reviewed the proposed carton/container labeling submitted on January 9, 2013, January 11, 2013 and January 17, 2013 and does not have any comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or [Sam.Skariah@fda.hhs.gov](mailto:Sam.Skariah@fda.hhs.gov).

If you have any questions on the PPI, please contact Kendra Jones at 301.796.3917 or [Kendra.Jones@fda.hhs.gov](mailto:Kendra.Jones@fda.hhs.gov).

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/s/  
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SAMUEL M SKARIAH  
01/18/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: January 18, 2013

To: Mary Parks, M.D., Director  
**Division of Metabolic and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Associate Director, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**

Melissa Hulett, RN, BSN, MSBA  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**

From: Twanda Scales, RN, MSN/Ed.  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name: KAZANO (alogliptin/metformin) Fixed-Dose Combination  
(FDC)

Dosage Form and Route: Tablets

Application  
Type/Number: NDA 203414

Applicant: Takeda Global Research and Development Center, Inc.

## 1 INTRODUCTION

On November 22, 2011, Takeda Global Research and Development Center, Inc. (Takeda) submitted for the Agency's review a New Drug Application (NDA 203424) for alogliptin/metformin FDC tablets for the treatment of Type 2 Diabetes. On February 2, 2012 the Division of Metabolic and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide for alogliptin/metformin FDC tablets. On April 23, 2012 Takeda submitted a Propriety Name Request for KAZANO which was concluded as acceptable by the Agency on July 20, 2012.

This review is written in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide for KAZANO (alogliptin/metformin) FDC tablets.

## 2 MATERIAL REVIEWED

- Draft KAZANO (alogliptin/metformin FDC) tablets Medication Guide (MG) received on November 22, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on January 7, 2013.
- Draft KAZANO (alogliptin/metformin FDC) tablets, Prescribing Information (PI) received on November 22, 2011, and received by DMPP January 7, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the MG is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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TWANDA D SCALES  
01/18/2013

MELISSA I HULETT  
01/18/2013

LASHAWN M GRIFFITHS  
01/18/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Memo**

Date: January 18, 2013

Reviewer: Reasol S. Agustin, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Yelena Maslov, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Nesina (Alogliptin) Tablets, 12.5 mg and 25 mg;  
Kazano (Alogliptin and Metformin) Tablets,  
12.5 mg/500 mg and 12.5 mg/1000 mg;  
Oseni (Alogliptin and Pioglitazone) Tablets,  
12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg,  
25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg

Application Type/Number: NDA 022271, NDA 203414, and NDA 022426

Applicant/sponsor: Takeda Pharmaceuticals America, Inc

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review evaluates the revised professional sample blister and bottle tray labeling for Nesina (Alogliptin) Tablets, 12.5 mg and 25 mg, Kazano (Alogliptin and Metformin) Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg, and Oseni (Alogliptin and Pioglitazone) Tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg submitted by the Applicant on January 17, 2013.

In this submission, the Applicant revised the trademark statement which is currently presented as “<TAKEDA PRODUCT> is a trademark of Takeda Pharmaceutical Company Limited and used under license by Takeda Pharmaceuticals America, Inc” to read “<TAKEDA PRODUCT> is a trademark of Takeda Pharmaceutical Company Limited registered with the U.S. Patent and Trademark Office and is used under license by Takeda Pharmaceuticals America, Inc.”

## **2 MATERIAL REVIEWED**

The revised professional sample blister and bottle tray labeling submitted to the Agency on January 17, 2013 were evaluated to assess whether the revision is acceptable from a medication safety perspective.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The revised professional sample blister and bottle tray labeling for Nesina (Alogliptin), Kazano (Alogliptin and Metformin), and Oseni (Alogliptin and Pioglitazone) submitted on January 17, 2013 are acceptable from the medication error perspective.

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/s/  
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REASOL AGUSTIN  
01/18/2013

YELENA L MASLOV  
01/18/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CONSULT REVIEW MEMO**

DATE: January 14, 2013

TO: Mehreen Hai and Richard Whitehead, Regulatory Project Managers  
Valerie Pratt, M.D. and Karen Mahoney, M.D. Clinical Reviewers  
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance

THROUGH: Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Treatment Assignment for Subject 8413-006/402

NDA: 22271

APPLICANT: Takeda Global Research and Development Center, Inc.

DRUG: Nesina (alogliptin)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: as an adjunct to diet and exercise to improve glycemic control in adults  
with type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: January 7, 2013

## I. BACKGROUND:

On January 7, 2013, the Office of Scientific Investigations (OSI) was requested to comment on treatment assignment for Subject 8413-006/402.

In April 2012, Takeda received a Complete Response letter from FDA for both the alogliptin and SYR-322-4833 NDAs, requesting additional clinical and postmarketing data to provide reassurance that alogliptin hepatotoxicity is of limited clinical significance. In response to this request, on July 26, 2012, Takeda submitted an updated safety profile of alogliptin with available data from recently completed and ongoing clinical trials along with additional postmarketing data from Japan. In Module 2.7.4 of the NDA resubmission, in-text Table 3.d, under “new case reported after May 15 2012” Subject 8413-006/402 (Subject 8413 at site 006 in study 402) is listed as alogliptin 25 mg.

On January 7, 2013, FDA DMEP review division received an e-mail from the sponsor informing the review division that the sponsor discovered an error in the treatment code and that Subject 8413-006/402 was randomized to placebo, not to alogliptin as originally reported in the NDA submission of July 26, 2012. The e-mail also contained an explanation for the error. The review division forwarded this e-mail to Office of Scientific Investigations (OSI) and requested advice from OSI concerning methods to determine the correct treatment assignment for the subject (**E-mail Attachment 1**). The sponsor discovered the error while they were in the process of updating Table 3f (Markedly abnormal values for hepatic parameters of Study 402). Takeda re-ran the table with a new database cut, with six months of additional data. Takeda attributes that error, 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 at the time of the NDA resubmission.

## II. RESULTS:

OSI requested and reviewed the following documentation and documents concerning this subject:

1. E-mails from Eugenio Andraca-Carrera and Mary Parks providing timelines for this subject and information that the subject started on treatment on November 16, 2011 and is randomized to placebo according to the dataset Sequence 0070 (71) submitted on 7/27/2012 (**E-mail Attachment 2**).
2. Takeda’s response to FDA information request submitted via e-mail on January 9, 2013 containing the case report form (CRF) and the site’s investigational product accountability log. The dosing log from Page 36 of the eCRF for Subject 8413-006 and the product accountability log (**Attachment 3**) were compared. All nine medication ID #'s on the subject eCRF are noted to be from placebo lots. In addition, included are two Takeda certificates of release for the bulk product lots that were dispensed to this subject, bulk lot Z641V081 and bulk lot 1025001A. The following are the nine “med ID#’s”:

- i. 22889862
- ii. 20117545
- iii. 22715106
- iv. 22068829
- v. 22128993
- vi. 21642842
- vii. 21945408
- viii. 220907254
- ix. 20660869

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data listing submitted to the NDA on June 27, 2012 and the additional documents submitted, specifically the eCRF and the medication log, demonstrate that the subject received placebo. The medication ID numbers entered in the CRF by the investigator are placebo lots per the site level inventory provided. This also matches Takeda's certificate of release for the drug lot as being placebo.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

# ATTACHEMENT 1

**Leibenhaut, Susan**


---

**From:** Parks, Mary H  
**Sent:** Monday, January 07, 2013 3:45 PM  
**To:** Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** RE: NDA22271 alogliptin: Information Request

[Correction - Jan 25th is the AGD](#)

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**From:** Parks, Mary H  
**Sent:** Monday, January 07, 2013 3:42 PM  
**To:** Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** FW: NDA22271 alogliptin: Information Request

Hi Susan

We have an unusual situation arise that I'm wondering if you can help advise us on. In the course of reviewing the NDA in this subject line we were down to a decision on approval for one case of liver toxicity in a clinical trial. We had numerous info requests on this case, including having this patient be called back in to have bloods drawn to rule out hepatitis. They did bring him back in and ruled out hepatitis E as a possible cause. Just today we got the email below telling us that they discovered an error in the treatment code and that this patient was randomized to placebo. Below are the company's explanations for this error, which essentially eliminated the safety concern. Frankly, I'm not able to verify their explanation below and this last minute discovery just makes me a little nervous, especially since they've known about this case for several months now and we've had several requests to them on him.

We have an opportunity to tcon w/ them so I was wondering from your experience w/ clinical site inspections are there specific documents you look at to make sure someone is randomized AND received treatment as reported to FDA? We have a AGD of Jan 29th so I seriously doubt OSI will be able to inspect this site (Russia) but any documentation that OSI can recommend we request be sent in would be helpful.

Thanks,  
Mary

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**From:** Whitehead, Richard  
**Sent:** Monday, January 07, 2013 10:40 AM  
**To:** Parks, Mary H; Pratt, Valerie  
**Cc:** Hai, Mehreen  
**Subject:** FW: NDA22271 alogliptin: Information Request

Mary,

Let me know if this answer your question or you want additional clarification.

Rich

---

**From:** Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]  
**Sent:** Monday, January 07, 2013 10:28 AM  
**To:** Whitehead, Richard  
**Cc:** Hai, Mehreen  
**Subject:** RE: NDA22271 alogliptin: Information Request

Dear Rich,

In the manually created in-text table of 2.7.4 of the NDA resubmission, Table 3.d, this subject (8413-006/402) was erroneously listed as alogliptin 25 mg. At the time of the resubmission, since this was a late breaker case (occurred after database cut-off), there was no program assisted narrative generated from the clinical database, which would have identified the subject treatment as placebo. In the clinical database, which is unblinded, this subject was correctly assigned to the placebo treatment arm in all the summary statistical tables (e.g., demographics, exposure, AEs and laboratory tables). We have validated the treatment assignment codes of the data and the IVRS randomization code which confirms this patient is indeed on the placebo treatment arm.

In the Pharmacovigilance safety database of SAEs, this subject still remains blinded. This case was not a SUSAR therefore was not unblinded for the purpose of an IND expedited safety report. All CIOMS for this subject indicate that the treatment code is not broken.

We would be glad to have a teleconference with the Agency to provide any additional details or clarity on this issue.

Kind regards,  
Sandy

Sandra D. Cosner, RPh  
Associate Director  
Regulatory Affairs

**Takeda Global Research & Development Center, Inc.**  
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Deerfield, IL 60015  
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[sandra.cosner@takeda.com](mailto:sandra.cosner@takeda.com)  
[www.tgrd.com](http://www.tgrd.com)

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**From:** Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]  
**Sent:** Monday, January 07, 2013 7:54 AM  
**To:** Cosner, Sandra (TGRD)  
**Cc:** Hai, Mehreen  
**Subject:** RE: NDA22271 alogliptin: Information Request

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](mailto:richard.whitehead@fda.hhs.gov)

---

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

Dear Rich,

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

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

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

Kind regards,  
Sandy

Sandra D. Cosner, RPh  
Associate Director  
Regulatory Affairs

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[sandra.cosner@takeda.com](mailto:sandra.cosner@takeda.com)  
[www.tgrd.com](http://www.tgrd.com)

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

Dear Sandy,

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

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

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

Parameter	Number (%) of Subjects With $\geq 1$ 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 EXAM NE."

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](mailto:richard.whitehead@fda.hhs.gov)

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The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and

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###

The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and

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# ATTACHEMENT 2

**Leibenhaut, Susan**


---

**From** Parks, Mary H  
**Sent** Tuesday, January 08, 2013 8:58 AM  
**To** Leibenhaut, Susan; Andraca-Carrera, Eugenio  
**Cc** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject** RE: NDA22271 alogliptin: Information Request

The patient was started on treatment on November 16, 2011. On study day 181 during a scheduled visit his ALT/AST values were found to be > 5xULN. On Study Day 187 he was subicteric w/ bili > 2xULN and ALT/AST now > 10xULN. So if we say about 6 months into the study, he was first noted to have liver abnormalities mid-May that progressed into June.

I don't recall when the report came in (Valerie - do you know?) but we have sent numerous info requests since then (and 7/27/12) so if they submitted to us in 7/27/12 that he was on placebo they certainly did divulge that info in the course of all the info requests.

---

**From:** Leibenhaut, Susan  
**Sent:** Tuesday, January 08, 2013 8:50 AM  
**To:** Parks, Mary H; Andraca-Carrera, Eugenio  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** RE: NDA22271 alogliptin: Information Request

Can you tell me the timeline for when the liver injury occurred/was reported relative to when the dataset was created submitted?  
Susan

---

**From:** Parks, Mary H  
**Sent:** Tuesday, January 08, 2013 8:42 AM  
**To:** Andraca-Carrera, Eugenio; Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** RE: NDA22271 alogliptin: Information Request

Thanks. This is helpful and is sufficient to convince me that he did receive placebo. If you told me a dataset was just submitted yesterday w/ this treatment assignment, I might push harder on the company.

How do others feel?

Mary

---

**From:** Andraca-Carrera, Eugenio  
**Sent:** Tuesday, January 08, 2013 8:22 AM  
**To:** Parks, Mary H; Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** RE: NDA22271 alogliptin: Information Request

Hi Mary

Patient 8413-006/402 was not included in the submission I used for my review of this application.

However, I found this patient in a SAS dataset submitted later to NDA 022426 Sequence 0070 (71) on 7/27/2012.

Patient 8413-006/402 is recorded as being randomized to Placebo QD.

---

**From:** Parks, Mary H  
**Sent:** Monday, January 07, 2013 7:25 PM  
**To:** Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer); Andraca-Carrera, Eugenio  
**Subject:** RE: NDA22271 alogliptin: Information Request

Susan

Thanks for the quick response w/ suggestion. I'm cc'ing Eugenio as he reviewed this trial for an interim CV analysis with the previous submission; however, it may be that this patient wasn't enrolled until after his review was completed as he started drug in Nov 2011.

Eugenio - you heard about this patient at today's labeling meeting. His patient ID number is **Patient 8413-006/402**  
Any possibility you can look at the SAS datasets to see if he's in there and can determine if he was assigned to pbo or alogliptin?

Thanks,  
Mary

---

**From:** Leibenhaut, Susan  
**Sent:** Monday, January 07, 2013 6:15 PM  
**To:** Parks, Mary H  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** RE: NDA22271 alogliptin: Information Request

All,

I was hoping to find some independent information, outside of Module 2, concerning this subject to determine treatment arm. However, I can't find it. It appears from the information below that this subject would be in the line listings in Study 402 Site 8413. The line listings for this site indicate only 2 subjects enrolled at this site. Subject 001 was in the Alogliptin arm and Subject 002 was not randomized. This study (the CV endpoint study) was ongoing at the time of submission, so I am assuming that the site was not yet fully enrolled when the initial line listings were submitted. **Is it possible that there is a SAS dataset with all enrolled subjects for this site that would contain treatment assignment in order to corroborate with the sponsor explanation?**

According to item below "in the manually created in-text table of 2.7.4 of the NDA resubmission, Table 3.d, this subject (8413-006/402) was erroneously listed as alogliptin 25 mg." Is this the Table on Page 53 of the July 17 resubmission in the ISS?

I will be discussing this issue with others in OSI to see if they can offer any insight into this or any suggestion for documents to request.  
Thanks,  
Susan

---

**From:** Parks, Mary H  
**Sent:** Monday, January 07, 2013 3:45 PM  
**To:** Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** RE: NDA22271 alogliptin: Information Request

[Correction - Jan 25th is the AGD](#)

---

**From:** Parks, Mary H  
**Sent:** Monday, January 07, 2013 3:42 PM  
**To:** Leibenhaut, Susan  
**Cc:** Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)  
**Subject:** FW: NDA22271 alogliptin: Information Request

Hi Susan

We have an unusual situation arise that I'm wondering if you can help advise us on. In the course of reviewing the NDA in this subject line we were down to a decision on approval for one case of liver toxicity in a clinical trial. We had numerous info requests on this case, including having this patient be called back in to have bloods drawn to rule out hepatitis. They did bring him back in and ruled out hepatitis E as a possible cause. Just today we got the email below telling us that they discovered an error in the treatment code and that this patient was randomized to placebo. Below are the company's explanations for this error, which essentially eliminated the safety concern. Frankly, I'm not able to verify their explanation below and this last minute discovery just makes me a little nervous, especially since they've known about this case for several months now and we've had several requests to them on him.

We have an opportunity to tcon w/ them so I was wondering from your experience w/ clinical site inspections are there specific documents you look at to make sure someone is randomized AND received treatment as reported to FDA? We have a AGD of Jan 29th so I seriously doubt OSI will be able to inspect this site (Russia) but any documentation that OSI can recommend we request be sent in would be helpful.

Thanks,  
Mary

---

**From:** Whitehead, Richard  
**Sent:** Monday, January 07, 2013 10:40 AM  
**To:** Parks, Mary H; Pratt, Valerie  
**Cc:** Hai, Mehreen  
**Subject:** FW: NDA22271 alogliptin: Information Request

Mary,

Let me know if this answer your question or you want additional clarification.

Rich

---

**From:** Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]  
**Sent:** Monday, January 07, 2013 10:28 AM  
**To:** Whitehead, Richard  
**Cc:** Hai, Mehreen  
**Subject:** RE: NDA22271 alogliptin: Information Request

Dear Rich,

In the manually created in-text table of 2.7.4 of the NDA resubmission, Table 3.d, this subject (8413-006/402) was erroneously listed as alogliptin 25 mg. At the time of the resubmission, since this was a late breaker case (occurred after database cut-off), there was no program assisted narrative generated from the clinical database, which would have identified the subject treatment as placebo. In the clinical database, which is unblinded, this subject was correctly assigned to the placebo treatment arm in all the summary statistical tables (e.g., demographics, exposure, AEs and laboratory tables). We have validated the treatment assignment codes of the data and the IVRS randomization code which confirms this patient is indeed on the placebo treatment arm.

In the Pharmacovigilance safety database of SAEs, this subject still remains blinded. This case was not a SUSAR therefore was not unblinded for the purpose of an IND expedited safety report. All CIOMS for this subject indicate that the treatment code is not broken.

We would be glad to have a teleconference with the Agency to provide any additional details or clarity on this issue.

Kind regards,  
Sandy

Sandra D. Cosner, RPh  
Associate Director  
Regulatory Affairs

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

One Takeda Parkway  
Deerfield, IL 60015  
U.S.A.  
T 224-554-1957  
M (b) (6)  
F 224-554-7870  
[sandra.cosner@takeda.com](mailto:sandra.cosner@takeda.com)  
[www.tgrd.com](http://www.tgrd.com)

---

**From:** Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]  
**Sent:** Monday, January 07, 2013 7:54 AM  
**To:** Cosner, Sandra (TGRD)  
**Cc:** Hai, Mehreen

**Subject:** RE: NDA22271 alogliptin: Information Request

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](mailto: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.**  
One Takeda Parkway  
Deerfield, IL 60015  
U.S.A.  
T 224-554-1957  
M (b) (6)  
F 224-554-7870  
[sandra.cosner@takeda.com](mailto:sandra.cosner@takeda.com)  
[www.tgrd.com](http://www.tgrd.com)

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

Dear Sandy,

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

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

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

Parameter	Number (%) of Subjects With $\geq 1$ 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 EXAM NE."

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](mailto:richard.whitehead@fda.hhs.gov)

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## ATTACHEMENT 3

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SUSAN LEIBENHAUT  
01/14/2013

SUSAN D THOMPSON  
01/14/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Memo**

Date: January 14, 2013

Reviewer: Reasol S. Agustin, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Yelena Maslov, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Nesina (Alogliptin) Tablets, 12.5 mg and 25 mg and  
Kazano (Alogliptin and Metformin) Tablets,  
12.5 mg/500 mg and 12.5 mg/1000 mg

Application Type/Number: NDA 022426 and NDA 203414

Applicant/sponsor: Takeda Pharmaceuticals America, Inc

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review evaluates the revised professional sample container label and carton labeling for Nesina (Alogliptin) Tablets, 12.5 mg and 25 mg and Kazano (Alogliptin and Metformin) Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant on January 9, 2013.

## **2 MATERIAL REVIEWED**

The revised professional sample container label and carton labeling submitted to the Agency on January 11, 2013 were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The revised professional sample container labels and carton labeling for Nesina (Alogliptin) and Kazano (Alogliptin and Metformin) submitted on January 11, 2013, address all of DMEPA's concerns and are acceptable from the medication error perspective.

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/s/  
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REASOL AGUSTIN  
01/14/2013

YELENA L MASLOV  
01/14/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: November 6, 2012

Reviewer: Reasol S. Agustin, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Yelena Maslov, PharmD  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Kazano (Alogliptin and Metformin) Tablets,  
12.5 mg/500 mg and 12.5 mg/1000 mg

Application Type/Number: NDA 203414

Applicant/Sponsor: Takeda Global Research and Development

OSE RCM #: 2011-4507

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Kazano (Alogliptin and Metformin) Tablets, NDA 203414, for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

The Applicant initially submitted the application for Alogliptin and Metformin Tablets under NDA 203414 on November 22, 2011. On August 16, 2012, the Applicant submitted a major amendment to this application providing updated clinical and postmarketing data that was submitted in the NDA 22-271 resubmission on July 26, 2012. The agency acknowledged this amendment on August 28, 2012.

On August 7, 2012, the Applicant submitted the container label, carton, and insert labeling for the proposed proprietary name, Kazano (Alogliptin and Metformin) Tablets to NDA 203414.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the May 1, 2012 submission.

- Active Ingredient: Alogliptin and Metformin
- Indication of Use: Adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 Diabetes Mellitus
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 12.5 mg/500 mg and 12.5 mg/1000 mg
- Dose and Frequency: One tablet twice daily with food; maximum dose of 25 mg per day of Alogliptin and 2000 mg per day of Metformin
- How Supplied: 60 count, 180 count, and 500 count bottles
- Storage: Store at 77° F, excursions permitted to 59° F to 86° F.
- Container and Closure Systems:
  - Bottles:
    - Commercial 60-count and 180-count and Professional samples 14-count bottle (b) (4): HDPE bottle (b) (4)
    - 500-count: (b) (4)
  - Blister: (b) (4)

## 2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Kazano labels and package insert labeling submitted by the Applicant.

### 2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 7, 2012 (Appendix A)
- Professional Sample Blister card Label submitted August 7, 2012 (Appendix B)
- Professional Sample Container Label submitted August 7, 2012 (Appendix C)
- Professional Sample Carton Labeling submitted August 7, 2012 (Appendix D)
- Insert Labeling submitted May 1, 2012 (no image)

## 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

- The Applicant proposes (b) (4) professional sample size (b) (4) 14-count. The (b) (4) 14-count would provide a supply of 7 days.  

- The Applicant uses a black colored font for the 12.5 mg/500 mg strength. This black text is (b) (4) difficult to read.

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## 4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

## 5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

### A. Comments Regarding Professional Sample Size

[REDACTED] (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 black-colored font is difficult to read [REDACTED] (b) (4)  
[REDACTED] 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

[REDACTED] (b) (4)  
The black-colored writing is difficult to read [REDACTED] (b) (4)  
[REDACTED] 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

[REDACTED] (b) (4)

The black-colored writing is difficult to read [REDACTED] (b) (4)

[REDACTED] While revising the background color, ensure there is sufficient differentiation between the two strengths of the product.

If you have further questions or need clarifications, please contact Margarita Tossa, Project Manager, at 301-796-4053.

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/s/  
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REASOL AGUSTIN  
11/06/2012

YELENA L MASLOV  
11/06/2012

CAROL A HOLQUIST  
11/06/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL INSPECTION SUMMARY

DATE: August 2, 2012

TO: Mehreen Hai, Regulatory Project Manager  
Valerie Pratt, Medical Officer  
Division of Metabolic and Endocrine Products

FROM: Janice Pohlman, M.D., M.P.H.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203414

APPLICANT: Takeda Global Research and Development Center, Inc.

DRUG: alogliptin/metformin  
NME: Yes  
THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Adjunct to diet and exercise to improve glycemic control in adults with  
type 2 diabetes mellitus [REDACTED] (b) (4)

CONSULTATION REQUEST DATE: January 18, 2012  
INSPECTION SUMMARY GOAL DATE: July 21, 2012 (extension to August 3, 2012)  
DIVISION ACTION GOAL DATE: September 22, 2012  
PDUFA DATE: September 22, 2012

## I. BACKGROUND:

Takeda Global Research and Development Center, Inc., seeks approval to market a fixed dose combination of alogliptin/metformin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

Alogliptin is a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4). DPP-4 rapidly degrades incretin hormones (glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic peptide (GDIP)). By preventing rapid degradation of these hormones, alogliptin enhances the body's ability to control elevated blood glucose by triggering pancreatic insulin secretion and suppressing pancreatic glucagon secretion. Alogliptin is a new molecular entity not commercially available in the U.S. Metformin targets insulin resistance by inhibiting hepatic glucose production and stimulating glucose uptake in skeletal muscle and adipose tissue, resulting in a long-term glucose lowering effect. Metformin is commercially available.

A single adequate and well-controlled study was submitted in support of this application.

### **SYR-322MET\_302**

The trial was designed as an international, multicenter, randomized, double-blind, and placebo-controlled Phase 3 trial. The trial included 7 treatment arms: placebo, alogliptin alone (12.5 mg BID and 25 mg QD), metformin alone (500 mg BID and 1000 mg BID), and the combination of alogliptin plus metformin (12.5 mg/500 mg BID and 12.5 mg/1000 mg BID). The primary objective of the trial was to evaluate the efficacy of the combination of alogliptin and metformin BID compared to alogliptin BID alone or metformin BID alone on HbA1c change from baseline at Week 26 (or Early Termination).

The total study duration was approximately 34 weeks, including a Screening Period ( $\leq 2$  weeks), a Placebo Run-in/Stabilization Period (4 weeks), a Double-Blind Treatment Period (26 weeks), and a Follow-Up Period (2 weeks) after the End-of-Study or Early Termination Visit.

The primary efficacy endpoint for the study was HgA1c change from baseline at Week 26 (or at time of discontinuation of double-blind study medication or hyperglycemic rescue).

A total of 198 study sites worldwide enrolled 784 subjects into the Treatment Period, with 109 to 114 subjects randomized to each of the 7 treatment groups

## II. RESULTS (by Site):

Name of CI Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Site #5301 Michael A. Szczesny, MD Boca Raton Clinical Research Associates, Inc. 600 South Dixie Highway, Suite 200 Boca Raton, FL 33432	SYR-322MET_302  27 subjects	March 19 – 22, 2012	NAI
CI#2: Site #5254 Dr. Bandgar Tushar Ramkrishna, MD, DM Research Health Institute in Diabetes, Endocrinology & Metabolism (RHIDEM) 1/15, Rupal Apartment, 3rd Floor Opposite Aroma Hotel, Dadasaheb Phalke Road Dadar, Mumbai 400 014, Maharashtra, India	SYR-322MET_302  20 subjects	July 16 - 19, 2012	*NAI (preliminary classification)

\*Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Site #5301: Michael A. Szczesny, MD  
Boca Raton Clinical Research Associates, Inc.  
600 South Dixie Highway, Suite 200  
Boca Raton, FL 33432
  - a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811 from March 19, to 22, 2012. For Study SYR-322MET\_302, at this site, 50 subjects were screened, 27 subjects were randomized, and 15 subjects completed the study. A 100% audit of screened subjects' informed consent documents was performed.

The study records of 20 randomized subjects were reviewed during the inspection. The record audit included comparison of case report form (CRF) source documents to eCRFs with particular attention paid to informed consent documentation, compliance with inclusion/exclusion criteria, laboratory results, and adverse event reporting. The FDA field investigator also evaluated Form FDA 1572s, principal investigator (PI) and sub-PI CVs, licenses, and financial disclosures, the drug accountability log and related records, sponsor

correspondence, IRB correspondence, site monitoring log and follow-up correspondence, appointment books, and recruitment materials.

- b. General observations/commentary: Source documents for randomized subjects whose records were reviewed were verified against the eCRFs. There were no serious adverse events at this site and all other AEs were documented, monitored, and reported within the required timeframe to the sponsor and IRB. The primary efficacy endpoints were verifiable for those subjects who completed this study.

No Form FDA 483 was issued at the conclusion of this inspection.

*OSI Reviewer Comment: Appendix 16.1.4.5 of the Clinical Study Report for SYR-322MET\_302 contains a "Note to File" from Takeda dated July 25, 2011. This document states that duplicate subjects were identified by (b) (4) (a contract research organization) by comparing demographic data of all enrolled subjects in the SYR-322MET\_302 study. These subjects, including subjects from Site #5301, either enrolled in the study at multiple sites (Subjects 5301004, 5301008, 5301010, 5301019, 5301020, 5301024, 5301032, 5301038, and 5301048) or participated in another study of alogliptin (SYR-322\_305) while enrolled in the SYR-MET\_302 study (Subjects 5301004, 5301015, 5301017, 5301041, and 5301050). These findings represent potential protocol violations of either exclusion criterion #15 (i.e. subject has received any investigational drug within the 90 days prior to screening) or receipt of a prohibited concomitant medication (i.e. another drug to treat diabetes mellitus). Whether a protocol violation actually occurred depended upon whether the subject received investigational drug from another site within 90 days of enrollment or whether they received simultaneous treatment for diabetes at another site and/or in another study.*

- *Example of a protocol violation: Subject #5301024 was screened at Site #5301 on 9/21/10 and entered the run-in phase on 9/24/10. However this subject had been screened, enrolled, and was receiving study treatment for diabetes at Site #5149 (subject #5149037) from 6/9/10 through 2/2/11.*
- *Example of where there was not a protocol violation at Site #5301: Subject #5301010 was screened at Site #5301 on 9/20/10, started the run-in period 9/23/10, and failed the run-in period 10/19/10. On 9/27/10 this subject presented to another site (Site # 5149) for the SYR-MET\_302 study and was determined to be a screen failure, and did not receive treatment for diabetes.*

*The "Note to File" further indicates that while blinded to treatment assignment, Takeda made the determination based upon the timing and nature of the simultaneous enrollment/treatment whether subjects should be included/excluded from the full analysis set, the per protocol set, or the safety set. The review division, DMEP, reviewed the sponsor's determinations and will consider these determinations in their overall analysis.*

The (b)(4) analysis and Takeda's determination of analysis set appear to be retrospective in nature. While the number of violations at this site suggests that the CI/site staff may not have been diligent about inquiring about participation in other investigational studies or concomitant administration of prohibited diabetes medications, there is no evidence based on inspectional findings to corroborate this.

- c. Assessment of data integrity: Notwithstanding the above discussion, the study appears to have been conducted adequately, and the data generated for subjects not identified above as duplicates may be used in support of the respective indication. The review division will consider the (b)(4) analysis and sponsor's determination of analysis set for each of the duplicate subjects noted above in their final review.

2. Site #5254: Dr. Bandgar Tushar Ramkrishna, MD, DM  
Research Health Institute in Diabetes,  
Endocrinology & Metabolism (RHIDEM)  
1/15, Rupal Apartment, 3rd Floor  
Opposite Aroma Hotel,  
Dadasaheb Phalke Road  
Dadar, Mumbai 400 014,  
Maharashtra, India

- a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811 from July 16, to July 19, 2012. Thirty six subjects were screened, 20 subjects were enrolled, and 19 subjects completed the study. The review of nine enrolled subjects' records included, but was not limited to, verification of the primary efficacy endpoint and occurrence of adverse events
- b. General observations/commentary: The records were readily available. There did not appear to be any pattern of omission of the data reported to the sponsor and FDA. The primary efficacy endpoint data were verifiable. There was no under-reporting of adverse events.
- c. Assessment of data integrity: The study appears to have been properly executed and the data generated by this site may be used in support of the pending application.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon full review of the EIR.

## IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Szczesny and Dr. Ramkrishna, were inspected in support of this NDA. Dr. Ramkrishna's site was NAI and the data generated by this site may be used in support of the pending application. Dr. Szczesny's site was not issued a Form FDA 483, however as noted in the discussion above, the clinical study report identified subjects who participated in the study at more than one site or in another study of alogliptin. The data for subjects not identified as duplicates may be used in support of the pending application. The review division will consider data from subjects identified as duplicates on an individual basis.

Note: Observations noted above for Dr. Ramkrishna's site are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

## CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE K POHLMAN  
08/02/2012

SUSAN D THOMPSON  
08/02/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: June 29, 2012

TO: Mary H. Parks  
Director,  
Division of Metabolism and Endocrinology Products

FROM: Gopa Biswas, Ph.D.  
Jyoti B. Patel, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.  
Chief, Bioequivalence Branch,  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

and

William H. Taylor, Ph.D., DABT  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 203-414, Alogliptin-  
Metformin FDC sponsored by Takeda Global Research and  
Development Center, Inc., USA

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC), conducted inspections of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** SYR-322MET\_101  
**Study Title:** "An Open-Label, Randomized, 2-Cohort, 4-Sequence, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin 6.25 mg and 12.5 mg and Metformin 500 mg and 1000 mg When Administered as Individual Tablets and as a Fixed-Dose Combination Tablet"

The study was conducted to assess the bioequivalence (BE) between individually administered immediate release metformin and alogliptin (reference) versus administration of combination of these drugs as test (SYR-322-Met-101, developed by Takeda) by pharmacokinetic analysis of SYR322 and metformin in human plasma samples as the primary objective. The secondary objectives were to assess safety and tolerability of these drugs administered individually or as FDC. During this study, 96 subjects were assessed for both BE and safety.

The audits of the clinical and analytical portions were conducted at PPD Phase-I Clinic, Austin, TX (May 14-21, 2012) conducted by ORA Investigator Todd R. Lorenz) (b)(4)

The audits included a thorough review of study records, examination of facilities and equipments, interviews and discussions with firms' management and staff.

Following the inspections, no significant objectionable conditions were observed at the analytical site and form FDA-483 was not issued; however, a form FDA-483 containing one observation was issued (**Attachment 1**) at the clinical site. A response to the inspectional observation was received from the clinical site on June 18, 2012 (**Attachment 2**). DBGC's evaluation of the inspectional observation and the firm's response follows:

**Clinical site: PPD Phase-I Clinic, Austin, TX:**

**Observation 1**

**Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically, concerning your clinical study of Takeda Protocol SYR-322MET-101 conducted from 5/5/2009-6/29/2009;**

(A) Source data pages 24-26 of the Data Collection Sheets (DCS) dated '04-Jun-2009' for Subject 1008/SJA were not present in the study files. This missing DCS pages were to record the Vital Signs and physical examination of the subject during the check-in process for Period 2 prior to dosing in treatment group C on 6/5/2009.

(B) Source data page 18 of the Data Collection Sheets (DCS) dated '07-Jun-2009' for Subject 2014/TDA was not present in

**the study files. This missing DCS page was to record the Vital Signs on Day 3 of Period 1 after dosing in Treatment Group F.**

In response to observations 1A and 1B, PPD acknowledged the deficiency and stated that the loss of the data collection sheets were noted in the footnotes and recorded as notes-to-file. A protocol deviation was also filed. Moreover, there were no serious adverse events reported and no clinically relevant abnormalities in vital signs were observed for the two subjects during the study. The DBGC reviewers are of the opinion that the deficiencies noted in observations 1A and 1B do not impact subject safety or compromise the integrity of the study. Therefore, PPD's response is acceptable.

**Conclusions:**

Following the above inspections, DBGC reviewers recommend that the data from clinical and analytical portions of study SYR-322MET\_101 can be accepted for further agency review.

Gopa Biswas, Ph.D.  
Jyoti B. Patel, Ph.D.  
Bioequivalence Branch, DBGC, OSI

**Final Classification:**

**VAI: PPD Phase-I Clinic, Austin, TX**

**FEI 3008374644**

**NAI:** [REDACTED] (b) (4)

**FEI** [REDACTED] (b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Dejernett

DBGC/BeB/Haidar/Dasgupta/Biswas/Patel

OND/ODEII/DMEP/Parks/Mehreen Hai

OCP/DCPII/Zhihong Li

OGROP/ORO/SW-FO/DAL-DO/DAL-IB/AUS-TX/Lorenz

ORA/[REDACTED] (b) (4)

Draft: GB 6/29/2012

Edit: JBP 7/3/2012, AD 7/05/2012

BE File # 6308; O:\BE\EIRCOVER\203414tak.met.alo.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1381132

8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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GOPA BISWAS

07/05/2012

Dr. Arindam Dasgupta signing on behalf of Dr. Sam Haidar

JYOTI B PATEL

07/05/2012

ARINDAM DASGUPTA

07/05/2012

Dasgupta signing on behalf of Dr. Sam Haidar

WILLIAM H TAYLOR

07/09/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # <b>203414</b> BLA# <b>N/A</b>	NDA Supplement #:S- <b>N/A</b> BLA STN # <b>N/A</b>	Efficacy Supplement Type SE- <b>N/A</b>
Proprietary Name: (b)(4) <b>(pending review)</b> Established/Proper Name: <b>Alogliptin/Metformin Hydrochloride Fixed-Dose Combination</b> Dosage Form: <b>Tablets</b> Strengths: <b>12.5 mg/500 mg and 12.5 mg/1000 mg</b>		
Applicant: <b>Takeda Global Research and Development Center, Inc</b> Agent for Applicant (if applicable): <b>N/A</b>		
Date of Application: <b>November 22, 2011</b> Date of Receipt: <b>November 22, 2011</b> Date clock started after UN: <b>N/A</b>		
PDUFA Goal Date: <b>September 22, 2012</b>		Action Goal Date (if different): <b>September 21, 2012</b>
Filing Date: <b>January 21, 2012</b>		Date of Filing Meeting: <b>January 10, 2012</b>
Chemical Classification (1,2,3 etc.) (original NDAs only) : <b>1, 4</b>		
Proposed indication(s)/Proposed change(s): <b>Treatment of Type 2 Diabetes Mellitus</b>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <b>N/A</b>
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <b>N/A</b>	
Resubmission after withdrawal? <input type="checkbox"/> <b>N/A</b>	Resubmission after refuse to file? <input type="checkbox"/> <b>N/A</b>	
Part 3 Combination Product? <input type="checkbox"/> <b>N/A</b>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other: <i>N/A</i>	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): <i>N/A</i>				
List referenced IND Number(s): <b>IND 069707 (alogliptin) and IND 101628 (alogliptin+metformin FDC)</b>				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<b>X</b>			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<b>X</b>			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<b>X</b>			<b>Standard Review</b>
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		<b>X</b>		
<i>If yes, explain in comment column.</i>			<b>X</b>	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			<b>X</b>	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<b>X</b>			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	N/A			
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			Submitted on 11/29/11
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			<b>X</b>	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			<b>X</b>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<b>X</b>			<b>PeRC scheduled for July 25, 2012</b>
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		<b>X</b>		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	YES	NO	NA	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			(b) (4) submitted with original application. (b) (4) submitted on 1/18/12
<b>REMS</b>	YES	NO	NA	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s): April 5, 2011</b>  <i>If yes, distribute minutes before filing meeting</i>	<b>X</b>			<b>Written response provided in lieu of meeting</b>
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		<b>X</b>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: **January 10, 2012**

BLA/NDA/Supp #: **NDA 203414**

PROPRIETARY NAME: (b) (4) **(pending review)**

ESTABLISHED/PROPER NAME: **Alogliptin-Metformin Fixed Dose Combination**

DOSAGE FORM/STRENGTH: **Tablets/ 12.5 mg/500 mg and 12.5 mg/1000 mg**

APPLICANT: **Takeda Global Research and Development Center, Inc**

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): **Treatment of Type 2 Diabetes Mellitus**

**BACKGROUND:** Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4) and was studied under IND 069707. The NDA (022271) for alogliptin was re-submitted on July 25, 2011, and is currently under review. Metformin (Trade name: Glucophage) is an anti-diabetic drug of the biguanide class and was approved by the FDA on March 3, 1995, under NDA 020357. Glucophage is marketed by Bristol-Myers Squibb, which has not given right-of-reference to Takeda. Takeda needs to rely on the Glucophage NDA for the safety and effectiveness of metformin, and therefore this NDA for alogliptin-metformin FDC is a 505(b)(2) application.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	<b>Mehreen Hai</b>	
	CPMS/TL:	<b>Julie Marchick</b>	
Cross-Discipline Team Leader (CDTL)	<b>Hylton Joffe</b>		
Clinical	Reviewer:	<b>Valerie Pratt</b>	
	TL:	<b>Hylton Joffe</b>	
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	<b>N/A</b>	
	TL:	<b>N/A</b>	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	<b>N/A</b>	
	TL:	<b>N/A</b>	

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Zhihong Li	
	TL:	Jaya Vaidyanathan	
Biostatistics	Reviewer:	Janice Derr	
	TL:	Todd Sahlroot	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	
	TL:	Todd Bourcier	
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Sheldon Markofsky	
	TL:	Suong Tran	
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Jamie Wilkins-Parker	
	TL:	Carlos Mena-Grillasca	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	

	TL:	N/A	
Bioresearch Monitoring (DSI)	Reviewer:	Jean Mulinde	
	TL:	Tejashri Purohit-Sheth	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Biopharmaceutics: Houda Mahayni (TL: Angelica Dorantes)		
Other attendees			

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>this drug/biologic is not the first in its class</li> <li>the clinical study design was acceptable</li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <b>Although alogliptin is an NME, it is fourth-in-class.</b>

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority: Curt Rosebraugh, M.D. (Office Director)</b>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Receipt Date:</b> November 22, 2012	
<b>60-day Filing Date:</b> January 21, 2012	
<b>74-Day Letter:</b> February 4, 2012	
<b>Standard Review 10-month Goal Date: September 22, 2012</b>	
Filing Mtg:	January 10, 2012
MCR Mtg:	May 1, 2012
Primary reviews complete:	July 28, 2012
Wrap up meeting:	TBD
PeRC meeting:	July 25, 2012
Secondary reviews complete:	August 4, 2012
Send labeling & PMR/PMCs to sponsor:	August 4, 2012
CDTL review complete:	August 11, 2012
Action package + letter to Div Dir.:	August 11, 2012
Action package + letter to ODE Dir.:	September 1, 2012
Sign Action Letter:	September 21, 2012
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.
	<u>Review Issues:</u>
	<input type="checkbox"/> No review issues have been identified for the 74-day letter.
	<input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <b>Comments provided by Clinical reviewer</b>
	<u>Review Classification:</u>
	<input checked="" type="checkbox"/> Standard Review
	<input type="checkbox"/> Priority Review

<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEHREEN HAI  
03/23/2012