

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201280Orig1s000

OTHER REVIEW(S)

Attachment B: Sample 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.

PMR/PMC Description: An epidemiologic study to compare the risk of severe hypersensitivity and severe cutaneous reactions in type 2 diabetics exposed to linagliptin to the risk in type 2 diabetics exposed to other antidiabetic medications.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>05/30/2012</u>
	Study/Trial Completion:	<u>11/30/2018</u>
	Final Report Submission:	<u>6/30/2019</u>
	Other:	<u>NA</u>

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

Linagliptin is a dipeptidyl peptidase (DPP)-4 inhibitor. Severe hypersensitivity reactions have been reported in the postmarketing setting for sitagliptin and saxagliptin, which are the only FDA-approved DPP-4 inhibitors. Some hypersensitivity reactions occurred in the linagliptin clinical development program. There were two cases of angioedema in patients on linagliptin; one of these was considered a serious adverse event. There were three cases of skin exfoliation that were considered possibly associated with linagliptin therapy; none was serious. Overall, the incidence of severe hypersensitivity reactions with linagliptin (if such an association exists) appears to be rare, but this study will help characterize this potential risk.

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.”

See response under Question 1. The goal of the epidemiological study is to compare the risk of severe hypersensitivity reactions and severe cutaneous reactions among type 2 diabetics exposed to linagliptin to those exposed to other antidiabetic medications.

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.

Risk of severe hypersensitivity reactions and severe cutaneous reactions.

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)
-

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?
-

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.*

(signature line for BLAs)

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/s/

AMY G EGAN
05/01/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: April 26, 2011

To: Raymond Chiang, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 201280 TRADENAME (linagliptin) Tablets
DDMAC's review of the carton container labeling for TRADENAME (linagliptin)

DDMAC has reviewed the proposed carton and container labeling for TRADENAME (linagliptin) submitted on March 17, 2011 and the blister labels submitted on March 25, 2011. DDMAC does not have any comments at this time.

Thank you for the opportunity to comment on these proposed materials. If you have any questions please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
04/26/2011

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.

PMR/PMC Description: A clinical pharmacology study in pediatric patients with type 2 diabetes to determine doses for the subsequent phase 3b study that will be conducted under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of linagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	11/30/2011
	Study/Trial Completion:	02/28/2014
	Final Report Submission:	08/31/2014
	Other:	N/A

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

Linagliptin 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 in pediatric patients ages 10 to 16 years (inclusive) with type 2 diabetes.

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 phase 1 pharmacokinetic dose finding study of linagliptin in pediatric patients ages 10 to 16 years (inclusive).
--

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)
Subpopulation: Pediatric patients ages 10-16 years (inclusive) with type 2 diabetes mellitus
-

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?

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.*

(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.

PMR/PMC Description: Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of linagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2014</u>
	Study/Trial Completion:	<u>03/31/2017</u>
	Final Report Submission:	<u>09/30/2017</u>
	Other:	<u>N/A</u>

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

Linagliptin 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 in pediatric patients ages 10 to 16 years (inclusive) with type 2 diabetes. The goal of the trial is to establish the safety and efficacy of linagliptin in this subpopulation.

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 randomized, double-blind, placebo-controlled and active-controlled clinical trial evaluating the efficacy, safety and pharmacokinetics of linagliptin in pediatric patients ages 10 to 16 years (inclusive). Treatment-naïve patients will be randomized to treatment with linagliptin, metformin and placebo in a 2:1:1 ratio (monotherapy setting). Patients inadequately controlled with metformin will be randomized to linagliptin or placebo (add-on to metformin setting). In the monotherapy setting, after an initial 12-week treatment period, patients treated with placebo will be randomized to treatment with linagliptin or metformin in a 2:1 ratio for 40 weeks. In the add-on to metformin setting, patients will be studied for 52 weeks, with the primary efficacy endpoint assessed at week 12.

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)
Subpopulation: Pediatric patients ages 10-16 years (inclusive) with type 2 diabetes mellitus

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?

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.*

(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.

PMR/PMC Description: A randomized, double-blind, placebo-controlled trial evaluating the effect of linagliptin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. Secondary objectives must include an assessment of the long-term effects of linagliptin on immunological reactions, hypersensitivity reactions, neoplasms, serious hypoglycemia, pancreatitis, and renal safety.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2012</u>
	Study/Trial Completion:	<u>10/31/2018</u>
	Final Report Submission:	<u>05/31/2019</u>
	Other:	<u>N/A</u>

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

Meta-analysis of the combined Phase 2 and Phase 3 premarketing clinical trials of linagliptin did not demonstrate an overall increased risk of major adverse cardiovascular events (MACE). However, the population studied had low baseline cardiovascular risk; few MACE occurred; the events were predominantly from the active control study; and the duration of blinded controlled study was not sufficient to address the risk definitively.

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.”

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry entitled "Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." This trial is intended to demonstrate that linagliptin does not increase the risk of major adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death).

The sponsor has already provided sufficient evidence that linagliptin does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded unacceptable cardiovascular risk to a magnitude needed for approved antidiabetic products. Therefore, consistent with the above guidance, the primary objective of the required postmarketing trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with linagliptin to that observed in the control group is less than 1.3.

Secondary objectives and adverse events of interest will include an assessment of the long-term effects of linagliptin on pancreatitis, renal safety, serious hypoglycemia, immunological reactions, and neoplasms. These are adverse events of interest based on data from clinical trials with linagliptin or other pharmacologically related products.

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 randomized, double-blinded, placebo-controlled cardiovascular outcomes trial to be conducted in patients with type 2 diabetes and increased cardiovascular risk. The primary endpoint will be the first occurrence of cardiovascular death, nonfatal myocardial infarction or stroke. Hospitalization for unstable angina will also be accepted as part of the endpoint. The trial will be event-driven, continuing until a sufficient number of events from the primary endpoint composite have occurred, in order for the trial to have adequate power to rule out an increase in risk of 30% for the primary endpoint. The trial will also have a minimum duration of follow-up of 400 weeks after randomization for each patient.

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)

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?
-

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.*

(signature line for BLAs)

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/s/

AMY G EGAN
04/25/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 4, 2011

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology

Through: Zachary Oleszczuk, Pharm.D., Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Addendum to February 14, 2011 Label and Labeling Review

Drug Name(s): Linagliptin Tablets, 5 mg

Application Type/Number: NDA 201280

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2010-2474-1

1 INTRODUCTION

This review summarizes DMEPA's evaluation of the revised blister labels submitted on March 25, 2011. The revisions were made in response to recommendations from DMEPA via email on March 17, 2011 (see Appendix A).

2 METHODS AND MATERIALS

DMEPA evaluated the revised sample blister labels (see Appendix B) for Linagliptin Tablets, 5 mg using Failure Mode and Effects Analysis (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors. Additionally, we evaluated the blisters to ensure DMEPA's recommendations have been implemented.

3 CONCLUSION

DMEPA finds the new sample blister labels acceptable and we have no additional comments. If you have any further questions or need clarifications on this review, please contact the OSE Project Manager Margarita Tossa at 301-796-4053.

Appendix A: Email Communications

RE: Carton, Container, and Blister labels-- nda201280 SDN 36—linagliptin

Hello all,

The information request was sent. The sponsor will resubmit the carton and container labels addressing our issues by next Thursday, March 31, 2011.

thanks,
ray

-----Original Message-----

From: Siahpoushan, Manizheh
Sent: Thursday, March 24, 2011 10:44 AM
To: Chiang, Raymond; Oleszczuk, Zachary; Markofsky, Sheldon B; Skariah, Sam
Cc: Tossa, Margarita; Sharma, Khushboo; Galliers, Enid M
Subject: RE: Carton, Container, and Blister labels-- nda201280 SDN 36-- linagliptin

Hello Raymond,

We have reviewed the new labels and labeling submitted on March 17, 2011, following our recommendations to the Applicant. Most of our recommendations have been addressed, however, in response to our recommendation (b) (4)

We find (b) (4) unacceptable. (b) (4)

We suggest replacing (b) (4) with the following statement: "No Tablet Here". This statement would minimize the risk of confusion created (b) (4). Additionally, this language has been used in the past in a similar situation.

Also, a quick note regarding the proprietary name review; although not communicated to the Applicant, the review is close to being finalized. We will notify you as soon as completed.

Please let me know if you have any questions.

Thanks,
Manizheh

Manizheh Siahpoushan, Pharm.D
Safety Evaluator
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-0340 (office)
manizheh.siahpoushan@fda.hhs.gov

-----Original Message-----

From: Chiang, Raymond
Sent: Thursday, March 17, 2011 4:22 PM

To: Siahpoushan, Manizheh; Oleszczuk, Zachary; Markofsky, Sheldon B; Skariah, Sam
Cc: Tossa, Margarita; Sharma, Khushboo; Galliers, Enid M
Subject: Carton, Container, and Blister labels-- nda201280 SDN 36-- linagliptin

Hello Manizheh, Zach, Sheldon and Sam,

Please see sponsor's response to your comments (see attachment) regarding their linagliptin carton and containers labels submitted on February 1, 2011. Please review these carton, container and blister labels and advise whether they are acceptable.

The edr link is provided below.

You can also access this submission via DARRTs (NDA 201280 SDN36).

thanks!

ray

Appendix B: Sample Blister Labels



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/s/

MANIZHEH SIAHPOUSHAN
04/04/2011

ZACHARY A OLESZCZUK
04/04/2011

CAROL A HOLQUIST
04/04/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: March 29, 2011

To: Raymond Chiang, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
Samuel Skariah, Regulatory Review Officer
Olga Salis, Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA 201280 TRADENAME[®] (linagliptin) tablets
DDMAC labeling comments for TRADENAME[®] (linagliptin) tablets

In response DMEP's July 28, 2010, consult request, DDMAC has reviewed the draft Patient Labeling (PPI) for TRADENAME[®] (linagliptin) tablets. Comments were previously provided on the Prescribing Information (PI) on March 14, 2011.

DDMAC's comments on the proposed PPI are based on the proposed draft marked version of the PPI titled, "11 0324 linagliptin 201280 DRISK PPI.doc" that was modified in the e-room on March 25, 2011 at 12:18 p.m. and the proposed draft marked version of the PI titled, "linagliptin PI.doc" that was modified in the e-room on March 25, 5:34 p.m.

DDMAC's comments on the PPI are provided directly in the marked version of the PPI below.

Thank you for the opportunity to comment on this draft PPI.

If you have any questions on the comments provided, please contact Kendra Jones at 301-796-3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
03/29/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: **March 24, 2011**

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Melissa Hulett, RN, BSN, MSBA
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Twanda Scales, MSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name PROPRIETARY NAME Pending (linagliptin)

Dosage Form and Route: 5 mg Tablets

Application Type/Number: NDA 201280

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2011-1624

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for linagliptin tablets. This product is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2 MATERIAL REVIEWED

- Draft linagliptin Patient Package Insert (PPI) received on July 2, 2010 and sent to DRISK on March 10, 2011.
- Draft linagliptin Prescribing Information (PI) received July 2, 2010 revised by the Review Division throughout the current review cycle and received by DRISK on March 10, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th 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 PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
03/24/2011

LASHAWN M GRIFFITHS
03/25/2011

**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS
SAFETY TEAM
MEMO TO THE FILE**

NDA/Submission #/Submission type: 201-280/000/N

Product Name: Linagliptin tablets, 5 mg

Application submission date: 2 July 2010

Safety team reviewer: Amy G. Egan, M.D., M.P.H.

Safety review completion date: 18 March 2011

Action goal date: 2 May 2011

Reason for Review: New Molecular Entity (NME) with proposed Patient Package Insert (PPI)

Items Reviewed: Draft Package Insert (PI); proposed PPI; Clinical review dated 3/13/2011

Synopsis of Findings: Linagliptin is an orally-active dipeptidyl peptidase 4 (DPP-4) inhibitor developed to improve glycemic control in adults with type 2 diabetes mellitus, as an adjunct to diet and exercise. Currently approved drugs in this class, and their dates of approval, include:

- **NDA 21-995 Januvia (sitagliptin)** – approved October 16, 2006
- **NDA 22-044 Janumet (sitagliptin/metformin HCl)** – approved March 30, 2007
- **NDA 22-350 Onglyza (saxagliptin)** – approved July 31, 2009
- **NDA 200-678 Kombiglyze XR (saxagliptin/metformin XR)** – approved November 5, 2010

Other related products in-house and under review include:



Currently labeled Contraindications for sitagliptin include: “hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema”.

Currently labeled Warnings and Precautions for sitagliptin include:

- Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.
- Dosage adjustment in patients with moderate or severe renal insufficiency and in patients with ESRD.
- Increased risk of hypoglycemia when added to an insulin secretagogue.
- Postmarketing reports of serious allergic and hypersensitivity reactions in patients, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.

The inclusion of pancreatitis in the PI for sitagliptin was based on post-marketing reports of acute pancreatitis, including necrotizing pancreatitis, and was required under the FDA Amendments Act (FDAAA), as was the conversion of the approved PPI to a Medication Guide (MG) with a Risk Evaluation and Mitigation Strategy (REMS). This was approved February 26, 2010.

Currently, a prior approval supplement (PAS) for sitagliptin providing for the addition of information regarding postmarketing reports of worsening renal function, including acute renal failure (sometimes requiring dialysis) to the Warnings & Precautions section of the PI, and corresponding modification to the MG and REMS, is pending approval.

There are no currently labeled contraindications for saxagliptin. Currently labeled Warnings and Precautions include:

- Increased risk of hypoglycemia when added to an insulin secretagogue.

There is no approved PPI, MG, or REMS for saxagliptin.

(b) (4)

The linagliptin clinical review noted the following:

- **Pancreatitis** was reported in a higher number of patients treated with linagliptin than placebo or other treatments (8 patients versus 0). In view of the large denominator, the imbalance of overall randomization (2.3:1) and the very small number of events of pancreatitis, the precise incidence rate of pancreatitis associated with linagliptin treatment is uncertain.
- **Hypersensitivity reactions** were reported by 6 patients (0.5%) in the placebo group and 18 patients (0.7%) in the linagliptin 5 mg group.
- Linagliptin is predominantly excreted unchanged in the feces, with renal excretion being a minor pathway of elimination. Pharmacokinetic studies and the clinical pharmacologist review of these studies conclude that dosage adjustment is not necessary in patients with **renal impairment**. The number of patients with moderate and severe renal disease is small in the clinical program. However, the applicant submitted 12 week data from a dedicated study in subjects with moderate to severe renal impairment and has one additional study ongoing in this

population. The results from these studies will shed further insight on the adverse event profile in these patients.

- The required **cardiovascular** meta-analysis was performed. This meta-analysis revealed that linagliptin is not associated with higher risk of predefined cardiovascular events.

Given the paucity of clinical trial data for linagliptin on the adverse events of special interest for DPP-4 inhibitors, and given the inconclusive nature at this time about the relative risk of these events among members of the drug class, I agree with the labeling as proposed by the clinical team:

- Under Contraindications: “TRADE is contraindicated in patients with a history of hypersensitivity reaction to linagliptin, such as urticaria, angioedema, or bronchial hyperreactivity.”
- Under Warnings & Precautions: “Insulin secretagogues are known to cause hypoglycemia. The use of TRADE in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial [see *Adverse Reactions (6.1)*]. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with TRADE.”

I also agree with the proposed PPI and do not recommend that the sponsor be required to convert the PPI to a MG, nor do I recommend any REMS for this product.

Determination:

REMS triggered: Y N I

If yes (Y) or indeterminate (I), was submission referred to the SRT: Y N

Date submitted: NA

Date response received: NA

SRT response: NA

If no (N), why not:

If no (N), please check one (or more) of the following reasons below:

No significant safety issue identified

Only editorial changes made

Changes pertain only to proper use of a device

Other:

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/s/

AMY G EGAN
03/17/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: March 14, 2011

To: Raymond Chiang, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 201280 TRADENAME (linagliptin) Tablets
DDMAC labeling comments for TRADENAME (linagliptin)

DDMAC has reviewed the proposed Prescribing Information (PI) for TRADENAME (linagliptin) accessed from the eRoom on March 8, 2011. DDMAC will provide its review of the patient information (PPI) on a later date.

General Comment

Comments regarding the PI are provided in the marked version of the PI below.

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.

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/s/

SAMUEL M SKARIAH
03/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 14, 2011
Application Type/Number: NDA 201280
To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis
From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Linagliptin Tablets, 5 mg
Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #: 2010-2474

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1 INTRODUCTION

This review evaluates the medication error potential of Boehringer Ingelheim Pharmaceuticals' container label and package insert labeling for Linagliptin Tablets.

1.1 REGULATORY HISTORY

Linagliptin Tablets 5 mg is a 505 (b) (1) application, NDA 0201280, submitted to the FDA on July 9, 2010.

DMEPA found the proprietary name Ondero unacceptable in RCM OSE Review #2010-1510 dated October 5, 2010, for this product. DMEPA held a teleconference on January 19, 2011 to discuss the name Tradjenta with the Applicant. DMEPA informed the Applicant that the name Trajenta is unacceptable due to the inclusion USAN stem -aj- in the name. Subsequent to that teleconference, the Applicant withdrew the name Trajenta and submitted the name Tradjenta for review on February 1, 2011. In this submission, the Applicant has also provided revised carton and container labeling for their primary proprietary name, Tradjenta. At this time, the proposed proprietary name, Tardjenta is pending Proprietary Name Review by DMEPA.

2 METHODS AND MATERIALS

We use Failure Mode and Effects Analysis¹ (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling. We provide recommendations that aim at reducing the risk of medication errors.

This review evaluates the linagliptin Tablets container label, Professional Sample blister and carton label, and package insert submitted by the Applicant on February 1, 2011. (See Appendix A for the container label and the professional sample blister and carton labeling images):

- Container Label: 30, 90, and 1000 tablets
- Container Label and Carton Labeling: 7 tablets (Rx sample)

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container label and package insert labeling identified deficiencies that can contribute to medication errors. Section 3.1 *Comments to the Division* contains our recommendations regarding package insert labeling that can be discussed in labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendation for the container labels and the carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Project Manager Margarita Tossa at 301-796-4053.

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.1 COMMENTS TO THE DIVISION

1. Replace all instances of the abbreviation “SU” with “sulfonylurea”. The Lexicon Medical Abbreviations reference, lists several meanings for the abbreviation “SU” such as Salicyluric Acid, Secretary Unit, Sensation Unit, Solar Urticaria, Sorbent Unit, Spectrophotometric Unit, Status Uncertain, Subunit, Sulfonamide, Suture, and Supine. Since the abbreviation “SU” does not have a single meaning, it may be misinterpreted and cause confusion.

Additionally, as part of a joint national campaign to reduce medication errors related to error prone medical abbreviations and dose designations, the FDA agreed not to approve labels and labeling that included the use of such error prone abbreviations. Therefore the abbreviation “SU” should be removed throughout all labels and labeling and replaced with “sulfonylurea”.

2. Highlights of Prescribing Information and Full Prescribing Information, *Dosage and Administration Section*

The statement “Take TRADE at approximately the same time each day” appears in Patient Information Section *How should I take TRADE?* This statement however, does not appear in the *Dosage and Administration Section*. If clinically significant, and in order to maintain consistency throughout the package insert, include the statement “Take TRADE at approximately the same time each day” in Highlights of Prescribing Information and Full Prescribing Information, *Dosage and Administration Section*.

3. We note that the Applicant removed the storage statement “excursions permitted to 15°C-30°C (59°F-86°F)” from the 30 and the 90 count containers and replaced with “(see insert)”, however, it remains on the 1000 count container. We believe this is inconsistent. We defer this issue to Chemistry.

3.2 COMMENTS TO THE APPLICANT

A. All Container Labels (30 tablets, 90 tablets, and 1000 tablets) and Carton Labeling (Rx sample)

Ensure the size of the established name is at least ½ the size of the letters comprising the proprietary name and both names are presented in a consistent font type in accordance with 21 CFR 201.10 (g)(2).

B. Carton Labeling (Rx sample)

1. Delete the first reference to “7 tablets” from the statement “7 tablets- 1 blister card of 7 tablets”, as this is a repetitive statement.
2. Revise the strength to state “5 mg per tablet”. This will clarify that 5 mg is contained in each tablet and not the total mg amount of all 7 tablets.
3. Remove the statement [REDACTED] ^{(b) (4)} as this is duplicative once the strength is revised to reflect “5 mg per tablet”.

C. Blister Foil Label

1. Remove (b) (4) from the empty cavities on the back of the sample blister foil labels. (b) (4)
(b) (4) If feasible, consider grouping (b) (4) together, and place the three empty cavities together. This configuration would minimize the risk of confusion created by having empty cavities in between cavities containing medication. Patients may misinterpret these empty cells (b) (4)
2. Remove (b) (4) from the blister foil labels. Linagliptin is a Once Daily medication used primarily by patients at home thus the (b) (4) are unnecessary and clutter the label.

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/s/

MANIZHEH SIAHPOUSHAN
02/14/2011

ZACHARY A OLESZCZUK
02/14/2011

CAROL A HOLQUIST
02/15/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 10, 2011

TO: Raymond Chiang, Regulatory Project Manager
Somya (Verma) Dunn, Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 201280

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG: Linagliptin

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

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

CONSULTATION REQUEST DATE: August 24, 2010

DIVISION ACTION GOAL DATE: May 2, 2011
PDUFA DATE: May 2, 2011

I. BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted NDA 201280 for a new molecular entity, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor for the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The applicant submitted the following 4 pivotal studies in support of the application:

- A. Protocol 1218.15 entitled “A Randomized, Double-blind, Placebo-controlled, Parallel-group 24 Week Study to Assess the Efficacy and Safety of BI 1356 (5 mg) in Combination with 30 mg Pioglitazone (Both Administered Orally Once Daily), Compared to 30 mg Pioglitazone Plus Placebo in Drug Naïve or Previously Treated Type 2 Diabetic Patients with Insufficient Glycemic Control”
- B. Protocol 1218.16 entitled “A Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of BI 1356 (5 mg Administered Orally Once Daily) Over 24 Weeks in Drug Naïve or Previously Treated (6 Weeks Washout) Type 2 Diabetic Patients with Insufficient Glycemic Control”
- C. Protocol 1218.17 entitled “A Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of BI 1356 (5 mg Administered Orally Once Daily) Over 24 Weeks in Type 2 Diabetic Patients with Insufficient Glycemic Control Despite Metformin Therapy” and
- D. Protocol 1218.18 entitled “A Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of BI 1356 (5 mg) Administered Orally Once Daily Over 24 Weeks in Type 2 Diabetic Patients with Insufficient Glycemic Control Despite a Therapy of Metformin in Combination with a Sulphonylurea.”

DSI received a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of the indication. Six foreign clinical investigator sites and the sponsor were inspected in support of this application. Clinical site selection was on the basis of high enrollment.

II. RESULTS (by Site):

Name of Clinical Investigator (CI), IRB, or Sponsor & Location	Protocol #/ # Subjects Randomized	Inspection Date	Final Classification
<u>CI</u> : Satoshi Inoue, M.D., Ph.D. OCROM Clinic, 4-12-11, Kasuga Suita-shi, Osaka 565-0853, Japan	Protocol 1218.15/ 35 subjects	November 1 to 5, 2010	VAI
<u>CI</u> : Osamu Matsuoka, MD ToCROM Clinic 6-26-8 Shinjuku, Shinjuku-ku Tokyo 160-0022, Japan	Protocol 1218.15/ 59 subjects	October 19 to 26, 2010	VAI
<u>CI</u> : Dr. Mathew Thomas Dept of Internal Medicine Kerala Institute of Medical Sciences P.B. No.1 Anayara P.O. Trivandrum – 695029, Kerala, India	Protocol 1218.16/ 24 subjects Protocol 1218.17/ 27 subjects	November 29 to December 3, 2010	VAI
<u>CI</u> : Dr. Sanjay Reddy Medisys Clinisearch India Pvt. Ltd. No 4C-426, 4th Cross, 2nd Block Kalyan Nagar, Bangalore – 560043, India	Protocol 1218.16/ 18 subjects Protocol 1218.17/ 24 subjects	December 6 to 10, 2010	NAI
<u>CI</u> : Diego Aizenberg, MD Centro Médico Viamonte Departamento de Nutrición, Metabolismo y Diabetología Capital Federal Avda Córdoba 2019, C1120AAB Buenos Aires, Argentina	Protocol 1218.18/ 40 subjects	December 13 to 17, 2010	NAI
<u>CI</u> : Jorge Waitman, MD Fundación Rusculleda & Battle, Departamento de Nutrición, Metabolismo y Diabetología Córdoba, Av Colón 2057 4to C 5000 Córdoba, Argentina	Protocol 1218.18/ 32 subjects	December 13 to 17, 2010	NAI
<u>Sponsor</u> : Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877		January 14, 19, 20 and February 3, 2011	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

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

1. Satoshi Inoue, M.D., Ph.D.

OCROM Clinic, 4-12-11, Kasuga, Suita-shi, Osaka 565-0853, Japan

- b. **What was inspected:** At this site, 37 subjects were screened, 35 subjects were randomized, and 34 subjects completed the study. An audit of all informed consents was performed. All randomized subjects' records were reviewed for verification of the primary efficacy endpoint. Full review of 22 subjects' records was conducted.

- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under-reporting of AEs. A Form FDA 483 was issued to Dr. Inoue for the regulatory violations of failure to adhere to the protocol in the following instances:
 - 1. The protocol required that trial medication be kept in recommended storage conditions, i.e. not above 25⁰C in order to protect from humidity and light. Study records fail to identify the date and time that study drugs were placed into storage, the location of the storage, and the temperature and humidity conditions under which the study drugs were held during shipment and storage. Through interview of study personnel, it appeared that drug was handled appropriately, but there was no documentation that this was the case. However, as the storage was to be at room temperature, and the storage conditions were reported as having been in room temperature settings, it is unlikely that this finding would impact stability of drug.

 - 2. Study records do not include all relevant correspondence between sponsor and study personnel and the e-mail correspondence was not printed or stored electronically with study records and that other correspondence including letters, meeting notes and notes of telephone calls were not all retained with study records.

Dr. Inoue responded adequately to the inspectional findings in a letter dated November 12, 2010.

- c. **Assessment of data integrity:** The above findings are considered minor and unlikely to impact data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Osamu Matsuoka, M.D.

ToCROM Clinic, 6-26-8 Shinjuku, Shinjuku-ku, Tokyo 160-0022, Japan

- a. **What was inspected:** At this site, 59 subjects were screened, 32 subjects were randomized, and 30 subjects completed the study. An audit of all informed consent documents was performed. All randomized subjects' records were reviewed for verification of the primary efficacy endpoint. Full review of 26

subjects' records was conducted.

- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under-reporting of AEs.

Inspection revealed that the trial site, ToCROM, is a dedicated clinical research site that maintains a database of potential candidates for clinical studies. Only 2 female subjects were enrolled in the study. One female was a screen failure due to disqualifying HbA_{1c} value at Visit 2 and the other (Subject 55204) was discontinued by the clinical investigator (CI) due to adverse event of edema and weight gain after Visit 4. During an interview with the FDA investigator, Dr. Matsuoka stated that, when he was provided with a list of potentially eligible subjects from the ToCROM database, he implemented an additional (undocumented) sorting process that removed any subjects that were experiencing edema at the time of the registration visits and removed subjects that had a BMI >30 because of the cautions in the Japanese label for the comparator product Actos (pioglitazone) regarding the side effect of edema occurring more frequently in women. The issue concerning edema in women was also discussed with the local IRB and the sponsor, who allowed for this variation on screening criteria as covered by the exclusion criterion concerning investigator judgment. Therefore, this observation was not cited as a violation.

A Form FDA 483 was issued for the violation of failure to maintain adequate and accurate records in the following instances:

1. There was no record of training having been provided to 11 personnel that several as clinical research coordinators (CRC) for the study.
2. Study records did not include documentation of the date or time that incoming shipments were placed into storage or the location where study drugs were stored upon receipt. Through interview of study personnel, it appeared that drug was handled appropriately, but there was no documentation that this was the case. However, as the storage was to be at room temperature, and the storage conditions were reported as having been in room temperature settings, it is unlikely that this finding would impact stability of drug.

Dr. Matsuoka adequately responded to the inspectional findings in a letter dated November 19, 2010.

- c. **Assessment of data integrity:** The above findings are considered minor and unlikely to impact data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. **Dr. Mathew Thomas**
Dept of Internal Medicine, Kerala Institute of Medical Sciences

P.B. No.1 Anayara P.O. Trivandrum – 695029, Kerala, India

- a. **What was inspected:** For Protocol 1218.16, at this site, 40 subjects were screened, 24 subjects were enrolled, and 22 subjects completed the study. For Protocol 1218.17, at this site, 40 subjects were screened, 27 subjects were enrolled, and 25 subjects completed the study. An audit of all informed consents was performed. A review of all subjects' records was conducted for verification of the primary efficacy endpoint. Full review of 18 subjects' records for each protocol was conducted to determine protocol adherence.
- b. **General observations/commentary:** The primary endpoint data were verified. The FDA inspection documented evidence of under-reporting of AEs for Protocol 1218.17 as noted below. In addition, a sponsor inspection conducted after the FDA investigation found additional data concerning rescue, concomitant medications, adverse events and existence of baseline conditions that had not been reported to the sponsor previously. A Form FDA 483 was issued to Dr. Thomas for the regulatory violations below:
 1. Failure to adhere to the protocol because seven unreported protocol deviations were found concerning the rescue of subjects without site confirmation of fasting blood sugar (FBS) values over 240 mg/dl. The majority of the decisions to rescue was based on elevated HbA_{1c} or elevated self-monitored glucose values. Of these seven violations, three subjects were not reported to the NDA as having been rescued.
 - a. For Protocol 1218.16, Subjects 67145 and 67164 assigned to the active treatment and Subjects 67152 and 67175 assigned to placebo were rescued. Subjects 67164 and 67152 were not reported to the NDA as having been rescued. Note that the randomization ratio for this study was 2:1 for active:placebo.
 - b. For Protocol 1218.17, Subjects 74001, 74018 and 74021, all assigned to active treatment were rescued. The rescue of Subject 74018 was not reported to the NDA. Note that the randomization ratio for this study was 3:1 for active:placebo.
 2. Failure to report AEs and concomitant medications because 5 subjects enrolled in Protocol 1218.17 took concomitant medications or had one or more instances of minor AEs including sore throat, urinary tract infections, epigastric tenderness, or fever that were not reported to the sponsor on the eCRFs. All these subjects were in the linagliptin group. Note that the randomization ratio for this study was 3:1 for active:placebo. The occurrence of this finding, limited to Protocol 1218.17, appeared to be due to the lack of structured source documents to record AEs and concomitant medications for this protocol.

Dr. Thomas responded adequately to the inspectional findings in a letter dated December 17, 2010.

A sponsor inspection conducted after the FDA investigation found additional data that had not been previously reported by the clinical site to the sponsor. The sponsor documents dated January 14, 2011 "Summary of unreported data at

site 91001” for each protocol, were collected by the FDA investigators during the sponsor inspection and were forwarded to the review division in an e-mail on February 9, 2011. Summary of the unreported data, including the unreported rescues above is as follows:

1. Three subjects from each protocol for whom rescue was not reported:
 - a. For Protocol 1218.16, Subjects 67164 and 67167 in the linagliptin group and Subject 67152 in the placebo group were not previously reported as having been rescued.
 - b. For Protocol 1218.17, Subjects 74018, 74027, and 74028, all in the linagliptin group were not previously reported as having been rescued.
 2. For both protocols, unreported concomitant therapy and adverse events (AEs) had not been reported. None of the AEs were considered serious and none led to discontinuation of medication. Most were related to hyperglycemia and the unreported rescues. Most concomitant medications that were not reported were associated with the unreported rescues.
 3. For both protocols, there were unreported baseline conditions. None of these conditions changed eligibility status of the subjects. Most conditions were related to previous surgeries or menopause.
- c. **Assessment of data integrity:** The above findings do not appear to be systematic. In spite of the imbalance in the randomization ratio, the effect of the unreported rescue on the outcome of the trial may be mitigated by the randomized double-blind superiority design of the trial. The violations are not considered to be significant and are unlikely to impact data reliability; however, this decision is deferred to the review division. In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. **Dr. Sanjay Reddy**

Medisys Clinisearch India Pvt. Ltd., No 4C-426, 4th Cross, 2nd Block Kalyan Nagar, Bangalore, 560043, India

- a. **What was inspected:** For Protocol 1218.16 at this site, 33 subjects were screened, and 17 subjects enrolled into the study. For Protocol 1218.17 at this site, 32 subjects were screened and 24 enrolled into the study. For both protocols, an audit of all enrolled subjects’ records was conducted. Review of 100% of informed consent documents was performed.
- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under-reporting of AEs. No significant violations were noted and a Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5. Diego Aizenberg, MD

Centro Médico Viamonte, Departamento de Nutrición, Metabolismo y Diabetología
Capital Federal, Avda Córdoba 2019, C1120AAB
Buenos Aires, Argentina

- a. **What was inspected:** For Protocol 1218.18, at this site, 56 subjects were screened and 40 were randomized into the study. Thirty-eight subjects completed the study. An audit of 33 subjects' records was conducted.
- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under-reporting of AEs. No significant violations were noted and a Form FDA 483 was not issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

6. Jorge Waitman, MD

Fundación Rusculleda & Battle, Departamento de Nutrición, Metabolismo y
Diabetología, Córdoba, Av Colón 2057 4to C
5000 Córdoba, Argentina

- a. **What was inspected:** At this site, 36 subjects were screened and 32 completed the study. An audit of 26 subjects' records was conducted.
- b. **General observations/commentary:** The primary endpoint data were verified. There was a single incidence of an AE characterized as "minor" in the records that was not reported to the sponsor (elevated blood pressure in Subject 80404, randomized to active treatment). No Form FDA 483 was issued. This was the only evidence of under-reporting of adverse events. No violations were cited and a Form FDA 483 was not issued.
- c. **Assessment of data integrity:** There was a single isolated incident of an elevated blood pressure that was not reported to the sponsor. This appears to have been an isolated incident and unlikely to impact data reliability. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

7. Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Rd., P.O. Box 368, Ridgefield, CT 06877

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change

upon receipt and review of the Establishment Inspection Report.

- a. **What was inspected:** This inspection covered sponsor activities for Protocols 1218.15, 1218.16, 1218.17, and 1218.18. The inspection reviewed the sponsor activities including organizational duties and responsibilities, monitoring activities including escalation policies and audits, adjudication procedures, adverse experience reporting, data collection and handling, and drug accountability. For the Dr. Thomas site, there was additional data presented from an internal sponsor review conducted after the FDA inspection of the clinical site. Because of the findings at Dr. Matsuoka's site in Tokoyo Japan additional information was requested concerning gender imbalance at Japanese sites.
- b. **General observations/commentary:** Monitoring procedures, escalation policies, and audit procedures appeared to be adequate. Adjudication of important cardiac and neurologic events appears to have been carried out in accordance with the charters of the respective entities.

Issues at Dr. Thomas' site were considered to be a case of inadequate local monitoring which appears to have been an isolated occurrence as documented by the sponsor. Sponsor has since returned to the site to perform 100% source data verification on 100% of the subjects. As noted on pages 5 and 6 under observations at Dr. Thomas's site, there were a total of 3 subjects whose rescue was not reported; and there were additional unreported data concerning adverse events and baseline data. In the re-analysis of the primary endpoint conducted by the sponsor using the additional rescue data, the treatment difference (Linagliptin-Placebo) for Protocol 1218.16 changed from -0.69 to -0.687 and for Protocol 1218.17 changed from -.066 to -0.65. This was not considered significant by the sponsor. See page 6 above for a discussion of the unreported AEs, concomitant medications, and baseline conditions. This re-analysis was provided to the review division.

The concerns expressed by the clinical investigators at the Matsuoka site regarding the safety of enrollment of female subjects into the trial due to the use of pioglitazone in the comparator arm of Study 1218.15 was known to the sponsor. The concerns were not expressed at any other site. The sponsor conducted additional analysis related to the gender imbalance and this was forwarded to the review division in an e-mail on February 9, 2011.

An FDA Form 483 was not issued.

- c. **Assessment of data integrity:** There was an isolated instance of inadequate monitoring at Dr. Thomas' site for Protocols 1218.16 and 1218.17. This did not appear to impact data integrity. The studies appear to have been conducted and monitored adequately, and the data submitted by the sponsor may be used in support of the respective indication.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator sites and the sponsor were inspected in support of this NDA. The primary endpoint data were verified. Inspection of Drs. Inoue, Matsuoka, and Thomas' sites noted violations that did not appear to be systemic or widespread in nature and no significant violations were noted at the other three clinical sites. The sponsor conducted an additional audit at the Thomas site. Data that was previously unreported to the sponsor was discovered concerning administration of rescue medication, adverse events, concomitant medications and baseline data; this was subsequently provided to DSI and forwarded to the review division. Except for the unreported rescue medication, the other issues were minor. The significance of the unreported rescue for the three subjects in each protocol is considered minor. Although some regulatory violations were noted as per above, these are considered isolated occurrences and are unlikely to significantly impact the integrity of primary efficacy and safety data overall. The data are considered reliable in support of the application.

Note: The final classification for the inspection of the sponsor is pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after receipt and review of the EIR for this inspection.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
02/11/2011

TEJASHRI S PUROHIT-SHETH
02/11/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Metabolism and Endocrinology Products

Application Number: NDA 201280

Name of Drug: Linagliptin Tablet

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): July 2, 2010

Receipt Date(s): July 2, 2010

Submission Date of Structure Product Labeling (SPL): July 2, 2010

Note to PM: If SPL has not been submitted, this must be listed as a deficiency under the Review section of this template. Also, note that lack of SPL is a deficiency that may result in a "Refuse to File" action (contact SEALD@FDA.HHS.GOV).

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

In this section, list any applicable format deficiencies that have been identified in the proposed labeling.

The following issues/deficiencies have been identified in your proposed labeling.

1. General Comments:
 - Use command language throughout the label.

- Please add line numbering to the Package Insert Word Document.

2. Highlights Section:

a. INDICATIONS AND USAGE:

- Please do not bullet/indent the indication statement or the “Important limitations of use” heading.
- Please add white space between indication statement and Important Limitations of Use.
- Please use bullets to itemize statements under the “Important limitations of use” heading. Please also capitalize the first letter of each statement (i.e. Should not be used in patients with type 1 diabetes.....).

b. CONTRAINDICATIONS:

- Please do not list theoretical possibilities (i.e. hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reactions.

3. Full Prescribing Information: Contents:

4. Full Prescribing Information (FPI):

a. DOSAGE FORMS AND STRENGTHS

- Please clarify in package insert whether “D5” is printed on one side and whether the Boehringer Ingelheim log is printed on the reverse side. See approved Onglyza package insert for appropriate language.

b. CONTRAINDICATIONS

- Please do not list theoretical possibilities (i.e. hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reactions. If no contraindications are known, this section must state “None”.

c. DRUG INTERACTIONS

- Please insert the cross references (i.e. *see Clinical Pharmacology (12.3)*) at the end of each paragraph.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by (date). This updated version of labeling will be used for further labeling discussions.

Raymond Chiang_____

NAME OF REGULATORY PROJECT
MANAGER
TITLE

Supervisory Comment/Concurrence:

Lina Aljuburi_____

NAME OF CHIEF PROJECT MANAGER
Chief, Project Management Staff

Drafted: RSC/DATE

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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

/s/

RAYMOND S CHIANG
10/07/2010

DSI CONSULT: Request for Clinical Inspections

Date: August 23, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Leibenhaut, M.D., DSI Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Somya (Verma) Dunn, M.D., Clinical Reviewer, DMEP, HFD-510
Ilan Irony, M.D., Clinical Team Leader, DMEP, HFD-510

From: Raymond Chiang, M.S., Consumer Safety Officer

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-201280

Applicant/ Applicant contact information (to include phone/email): Boehringer Ingelheim
Pharmaceuticals, Inc. /Maureen Oaks, Pharm.D. Associate Director; (ph) 203-798-5723
(email)Maureen.Oaks@boehringer-ingelheim.com

Drug Proprietary Name: Proposed Name is ONDERO

NME or Original BLA (Yes/No): Yes; please see eCTD sequence number 0000 and sequence number 0004 associated with NDA 201280

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

PDUFA:

Action Goal Date: May 2, 2011

Inspection Summary Goal Date: February 22, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>Site# DE000980 Matthew Thomas, MD</p> <p>Dept of Internal Medicine KIMS, Kerala Institute of medical Sciences, P.B.No.1 Anayara P.O. Trivandrum - 695029, Kerala, India, Phone # +91 471 2446490 Mobile No.: +91 9447753533, Email amnavita@gmail.com or amnavita@asianetindia.com, Fax # +91 471 244 6460)</p>	1218.16	24 randomized	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<p>Site# DE000983 Sanjay Reddy, MD</p> <p>Medisys Clinisearch India Pvt. Ltd., No 4C-426, 4th Cross,2nd Block Kalyan Nagar, Bangalore – 560043, India, Phone # +91 80 25421333 or +91 80 23479424 or +91 25457022, Email contact@bangalorediabetescentre.com or drsanjaycreddy@yahoo.com, Fax # +91 80 25425396</p>	1218.16	18 randomized	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<p>Site # NB00277 Satoshi Inoue, MD, PhD</p> <p>Medical Corporation Heishinkai OCROM Clinic 4-12-11,Kasuga,Suita-shi,Osaka 565-0853 Japan, Phone # +81 6 6330 8810, Email satoshi.inoue@ocrom.jp Fax # +81 6 6330 8801</p>	1218.15	35 randomized	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>Site# NB000275 Osamu Matsuoka, MD</p> <p>ToCROM Clinic 6-26-8 Shinjuku, Shinjuku-ku, Tokyo 160-0022, Japan, Phone # +81 3 5285 2150, Email osamu_matsuoka@tocrom.jp, Fax # +81 3 5285-2159</p>	1218.15	32 randomized	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<p>Site# UKDE9501 Diego Aizenberg, MD</p> <p>Centro Médico Viamonte Departamento de Nutrición, Metabolismo y Diabetología Capital Federal, Buenos Aires Avda Córdoba 2019 C1120AAB Capital Federal Buenos Aires, Argentina, Phone # +54 (11) 49635650 or +54 (11) 49635649, Email diegoaiz@fibertel.com.ar Fax # +54 (11) 49618021</p>	1218.18	40 randomized	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
<p>Site# UKDE9550 Jorge Waitman, MD</p> <p>Fundación Ruscullada & Battle Departamento de Nutrición, Metabolismo y Diabetología Córdoba, Córdoba Av Colón 2057 4to C 5003 Córdoba, Argentina, Phone # +54 (341) 4888200, Email cwaitman@arnet.com.ar, Fax # +54 (341) 4683632</p>	1218.18	32 randomized	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

Page 4-Request for Clinical Inspections

These sites have the highest subject enrollment and some of these sites participated in more than one pivotal clinical trial.

Please focus on during inspections the confirmation of the appropriateness of referrals of CV events from each site. There are very few MACE events in the overall program (total n=34, 23 in control, 11 in lina), and it is important to be thorough in the few sites selected that we look at this.

Also of consideration is to determine whether there is UNDER-reporting or a cultural difference among the sites that may affect the interpretability of safety and / or efficacy of linagliptin, as well as acceptability of these data to the US diabetic population.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) ---- Please focus on during inspections the confirmation of the appropriateness of referrals of CV events from each site. There are very few MACE events in the overall program (total n=34, 23 in control, 11 in lina), and it is important to be thorough in the few sites selected that we look at this.

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *These sites have the highest enrollment.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Raymond Chiang 301-796-1940 or Somya (Verma) Dunn at 301-796-3829.*

Concurrence: (as needed)

Ilan Irony
Somya (Verma) Dunn
Mary Parks

Medical Team Leader
Medical Reviewer
Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201280	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	Linagliptin (BI 1356) Tablets.

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

/s/

RAYMOND S CHIANG
08/24/2010

AMY G EGAN
08/24/2010
Amy Egan for Mary Parks

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201280 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proposed Proprietary Name: Ondero (trade name review pending) Established/Proper Name: Linagliptin Dosage Form: Immediate release tablet for oral administration Strengths: 5 mg		
Applicant: Boehringer Ingelheim Pharmaceuticals Inc. Agent for Applicant (if applicable):		
Date of Application: July 2, 2010 Date of Receipt: July 2, 2010 Date clock started after UN:		
PDUFA Goal Date: May 2, 2011		Action Goal Date (if different):
Filing Date: August 31, 2010		Date of Filing Meeting: August 9, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with type 2 diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<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:	<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): N/A				
List referenced IND Number(s): (b) (4)				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	Yes			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, 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>	Yes			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	Yes			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		No		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	Yes			
<u>User Fee Status</u> <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 UN letter and contact user fee staff.</i>	Payment for this application: <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			
 <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>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			N/A																	
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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			N/A																	
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))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			N/A																	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:			N/A																	
<table border="1"> <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																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<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>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		No																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	Yes			Request located in eCTD Module 1.3.5.3																

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		No		
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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<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)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	Yes			Invite eCTD support staff to filing meeting
Index: Does the submission contain an accurate comprehensive index?	Yes			
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: <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) If no , explain.	Yes			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>		No		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			N/A	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p>	Yes			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	Yes			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>Is patent information submitted on form FDA 3542a?</p>	Yes			
Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	Yes			FDA 3454 included
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p>	Yes			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act 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>	Yes			Applicant is located in US; patent holder is in Germany.

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: 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>			N/A	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	Yes			Awaiting confirmation of NDA scheduled for March 2011 PeRC meeting
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	No			Millie Wright (Pediatric group) will add language to 74-day letter
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	No			Millie Wright (Pediatric group) will add language to 74-day letter
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	No			Millie Wright (Pediatric group) will add language to 74-day letter
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>	No			

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	Yes			DDMAC does not have any promotional issues with Ondero. Awaiting final decision by OSE.
Prescription Labeling	<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	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	Yes			
Is the PI submitted in PLR format?	Yes			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			N/A	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	Yes			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	Yes			Consult sent to OSE to review PI, PPI, and carton and container
REMS consulted to OSE/DRISK?		N/A		No REMS
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	Yes			Consult sent to OSE to review PI, PPI, and carton and container
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	N/A			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	N/A			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	N/A			
Consults	YES	NO	NA	Comment
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>		No		As discussed during filing meeting, QT-IRT was consulted on 10.23.09.

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): December 11, 2007 <i>If yes, distribute minutes before filing meeting</i>	Yes			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 2, 2009 <i>If yes, distribute minutes before filing meeting</i>	Yes			
Any Special Protocol Assessments (SPAs)? Date(s): Clinical SPA submitted 2.6.09; FDA response on 2.17.09 denying request. FDA provided comments to Clinical SPA on 3.30.09. Special Protocol/Carcinogenicity submitted 4.21.06 (SDN 18 and 19). FDA response on 5.13.08 and 6.13.08 with AI Letters. <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				Carcinogenicity Datasets submitted sequence number 0001

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8.9.10

BLA/NDA/Supp #: NDA 201280

PROPRIETARY NAME: Ondero

ESTABLISHED/PROPER NAME: Linagliptin

DOSAGE FORM/STRENGTH: Immediate release tablet for oral administration/ 5mg

APPLICANT: Boehringer Ingelheim Pharmaceuticals Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with type 2 diabetes mellitus

BACKGROUND: This is a new molecular entity (NME), a third in class dipeptidyl peptidase-4 (DPP-4) inhibitor, developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The dosage form and strength are 5 mg tablets. The recommended dose is 5 mg once daily.

Summary of trials whose results are used to support the efficacy in the sponsor proposed labeling:

Study	Treatments	Duration	Centers (countries)	n
1218-15	Lina + Pioglitazone	24-WK	43 (7)	252
	PBO + Pioglitazone			128
1218-16	Lina	24-WK	66 (11)	333
	Placebo			163
1218-17	Lina + Met	24-WK	82 (10)	513
	Placebo + Met			175
1218-18	Lina + Met + SU	24-WK	100 (11)	778
	Placebo + Met + SU			262
1218-20	Lina + Met	52-WK	209 (16)	766
	Glimepiride + Met			761
1218-35	Lina + SU PBO + SU	18-WK	45 (7)	158
	Lina			82
1218-50	PBO(in Met- intolerant patients)	18-WK	53 (7)	147
				73

*Studies 1218-15,-16,-17, and -18 were pivotal double blind placebo-controlled trials.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Raymond Chiang	Yes
	CPMS/TL:	Lina Aljuburi	Yes
Cross-Discipline Team Leader (CDTL)	Ilan Irony		
Clinical	Reviewer:	Somya (Verma) Dunn	Yes
	TL:	Ilan Irony	Yes
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC</i>	Reviewer:	N/A	

<i>products)</i>			
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Lokesh Jain	Yes
	TL:	Sally Choe	No
Biostatistics	Reviewer:	Wei Liu; Xiao Ding- to review meta-analyses of CV risk endpoints	No
	TL:	Jon T. Sahlroot; Mat Soukup- TL for Xiao Ding	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	Yes
	TL:	Todd Bourcier	No
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman	No
	TL:	Karl Lin	No
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Suong Tran	Yes
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Not required as per CMC reviewer	
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	Steve Hertz, Shawn Gould, Jaewon Hong (DMPQ)	Yes; Shawn Gould attended
	TL:	Tara Goen	
OSE/DMEPA (proprietary name)	Reviewer:	Tara Turner (proprietary trade name) Carton and container	No; Margarita Tossa

			(OSE RPM) attended the filing meeting
	TL:	Zach Oleszczuk (proprietary trade name) Carton and container	No; Margarita Tossa (OSE RPM) attended the filing meeting
OSE/DRISK (REMS)	Reviewer:	Melissa Hulett	No
	TL:	LaShawn Griffiths	No
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	No
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<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"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</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"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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>CLINICAL PHARMACOLOGY</p> <p>Comments:</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"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</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>NONCLINICAL</p>	<input type="checkbox"/> Not Applicable

<p>(PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</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>PRODUCT QUALITY (CMC)</p> <p>Comments:</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><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: As per CMC filing review, the EA categorical exclusion to be reviewed by primary CMC reviewer.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: CMC reviewer stated quality microbiology reviewer not needed</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curtis Rosebraugh	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<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"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • 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) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201280	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	Linagliptin (BI 1356) Tablets.

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

/s/

RAYMOND S CHIANG
08/23/2010