

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201281Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 201281	NDA Supplement #: N/A	Efficacy Supplement Type: N/A
Proprietary Name: TBD Established/Proper Name: Linagliptin/Metformin Hydrochloride Fixed-Dose Combination Dosage Form: Tablets Strengths: 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.		
Date of Receipt: January 19, 2011 (resubmitted on November 30, 2011 after Complete Reponse issued on November 16, 2011)		
PDUFA Goal Date: January 30, 2012		Action Goal Date (if different):
Proposed Indication(s): Treatment of Type 2 Diabetes Mellitus		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

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

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Glucophage (metformin hydrochloride) tablets (NDA 020357)	Safety and efficacy data throughout US Prescribing Information
Published literature	Use in Specific Populations - Pregnancy (Section 8.1 of label)

*each source of information should be listed on separate rows

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

BA/BE studies for Glucophage

RELIANCE ON PUBLISHED LITERATURE

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

YES ☒ NO ☐

If “NO,” proceed to question #5.

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

YES ☐ NO ☒

If “NO”, proceed to question #5.

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

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

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

If "NO," proceed to question #10.

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

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

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

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

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

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

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

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

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

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

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

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

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

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

Pharmaceutical equivalent(s): **N/A**

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

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

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

YES ☐ NO ☒

If **“NO”**, proceed to question #12.

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

YES ☐ NO ☐

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

YES ☐ NO ☐

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

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

Pharmaceutical alternative(s): **N/A**

PATENT CERTIFICATION/STATEMENTS

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

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

No patents listed ☒ *proceed to question #14*

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

YES ☐ NO ☐

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

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

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

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

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

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

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

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

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

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

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

Method(s) of Use/Code(s):

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

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

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

YES ☐ NO ☐

If “NO”, please contact the applicant and request the signed certification.

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

YES ☐ NO ☐

If “NO”, please contact the applicant and request the documentation.

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

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

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

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

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

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/s/

MEHREEN HAI
01/25/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: November 3, 2011

To: Mehreen Hai, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kendra Jones, Regulatory Review Officer, OPDP
Olga Salis, Regulatory Project Manager, OPDP
Lisa Hubbard, Team Leader - Professional Review Group 3, OPDP

Subject: NDA 201281 TRADE (linagliptin and metformin HCl) tablets

OPDP labeling comments for TRADE (linagliptin and metformin HCl) tablets

OPDP has reviewed the proposed Prescribing Information (PI) for TRADE accessed from the eRoom on 11/01/11:

(http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_2561f)

In addition, OPDP has reviewed the carton and container labeling submitted by the sponsor on 01/19/11:

(\\Cdsesub1\evsprod\NDA201281\201281.enx)

OPDP's comments regarding the PI are provided in the marked up version below. OPDP does not have any comments regarding the proposed carton and container labeling. Comments regarding the patient package insert (PPI) will be provided in a separate memo at a later date.

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

If you have any questions on the PI, please contact Sam Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

17 pages of draft labeling has been withheld
in full as B(4) CCI/TS immediately
following this page

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/s/

SAMUEL M SKARIAH
11/03/2011

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

Label and Labeling Review

Date:	October 28, 2011
Reviewer	Terri Wood-Cummings, MD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Carlos Mena-Grillasca, RPh Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths	(b) (4) (Linagliptin and Metformin Hydrochloride) Tablets 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg
Application Type/Number	NDA 201281
Sponsor	Boehringer Ingelheim
OSE RCM #:	2011-353

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

1 INTRODUCTION

This review evaluates the proposed container labels and Prescribing Information labeling for (b) (4) (Linagliptin and Metformin) and its vulnerability to medication errors.

1.1 BACKGROUND

The proposed proprietary name, (b) (4) is currently under review (OSE RCM #2011-3166).

1.2 PRODUCT INFORMATION

(b) (4) is a dipeptidyl peptidase-4 (DDP-4) inhibitor and biguanide fixed combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate. The product will be available in three combination strengths of linagliptin and metformin hydrochloride (2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg). The recommended dose is one tablet by mouth twice a day with meals. Gradual dose escalation is recommended to reduce gastrointestinal side effects due to metformin. The maximum recommended dose is 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. All dosing strengths will be available in 14 count sample bottles and retail bottles of 60, 180, and 2000 tablets. The bottles should be stored at 25°C (77°F), with excursions permitted to 15-30°C (75°F -86°F) and protected from exposure to high humidity.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and our learning from postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container labels submitted August 17, 2011 (Appendix A)
- Insert labeling submitted August 3, 2011 (no image)

3 CONCLUSIONS AND RECOMMENDATIONS

The container labels require revision prior to approval. See Section 3.1 (*Comments to the Sponsor*). We request these be communicated to the Sponsor prior to approval.

DMEPA's comments on the Insert labeling are included in Section 3.2 and will be discussed during the labeling meetings.

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

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

3.1 COMMENTS TO THE SPONSOR

A. CONTAINER LABELS (ALL STRENGTHS; 14, 60, 180, AND 2000 COUNT BOTTLES)

1. Revise the “Usual Dosage” statement to read: “Usual Dosage: See prescribing information.”

B. CONTAINER LABELS (ALL STRENGTHS; 60, 180, AND 2000 COUNT BOTTLES)

1. Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxx-XXXX-xx). Pharmacists use this portion of the NDC number to ensure the correct product is dispensed.

C. CONTAINER LABELS (ALL STRENGTHS; 60 AND 180 COUNT BOTTLES)

1. Delete the statement (b) (4)
(b) (4) This statement could be confusing
to pharmacists (b) (4)

D. CONTAINER LABELS (ALL STRENGTHS; 2000 COUNT BOTTLES)

1. Delete the statement (b) (4)

E. ALL CONTAINER LABELS FOR THE 2.5 MG/850 MG AND 2.5 MG/1000 MG STRENGTHS

1. Revise the color blocking scheme used to highlight the strength statement on the 2.5 mg/850 mg (i.e. royal blue) and the 2.5 mg/1000 mg (b) (4) labels to provide adequate differentiation between the two strengths. The current color blocking scheme are similar in color and matched to the bar graphics making it difficult to differentiate between the two strengths.

3.2 COMMENTS FOR THE INSERT LABELING FOR DISCUSSION DURING THE LABELING MEETINGS

A. FULL PRESCRIBING INFORMATION

1. Dosage and Administration Section 2.1 includes a list of the available dosage tablet strengths. This information is pertinent and already included in the Dosage Forms and Strengths Section 3 of the PI and is therefore redundant. Revise to delete the statement that reads (b) (4)

2. Section 16 (How Supplied/Storage and Handling) includes statements which describe the physical appearance for each tablet strength. These statements are pertinent to and included in the Dosage Forms and Strengths Section of the PI; therefore, they are redundant and we recommend deleting them. Then, revise each of the statements which begin (b) (4) to read:

“TRADE tablets (linagliptin and metformin HCl) 2.5 mg/500 mg are supplied as follows...”

“TRADE tablets (linagliptin and metformin HCl) 2.5 mg/850 mg are supplied as follows...”

and “TRADE tablets (linagliptin and metformin HCl) 2.5 mg/1000 mg are supplied as follows...”

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/s/

TERRI WOOD-CUMMINGS
10/31/2011

CARLOS M MENA-GRILLASCA
10/31/2011

CAROL A HOLQUIST
10/31/2011

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

PATIENT LABELING REVIEW

Date: **October 28, 2011**

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

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

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

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

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

Drug Name (established name): TRADE (linagliptin and metformin hydrochloride)

Dosage Form: Tablets

Application Type/Number: NDA 201281

Applicant: Boehringer Ingelheim

OSE RCM #: 2011-354

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 TRADE (linagliptin and metformin hydrochloride). The purpose of the Applicant's submission is to provide an amendment to its 505(b)(2) New Drug Application (NDA 201281) and to revise proposed draft labeling. Additionally, the Applicant proposes updating the draft linagliptin and metformin prescribing information to be consistent with the approved Tradjenta (linagliptin) label.

2 MATERIAL REVIEWED

- Draft TRADE (linagliptin and metformin hydrochloride) tablets, Patient Package Insert (PPI) received on August 3, 2011 and received by DRISK on October 20, 2011.
- Draft TRADE (linagliptin and metformin hydrochloride) tablets, Prescribing Information (PI) received August 3, 2011 revised by the Review Division throughout the current review cycle and received by DRISK on October 20, 2011.
- Approved Trajenta (linagliptin), comparator labeling, dated May 2, 2011.
- Approved Glumetza (metformin hydrochloride extended-release), comparator labeling, dated April 13, 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)
- rearranged information due to conversion of the PI to PLR format
- 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)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

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
10/28/2011

LASHAWN M GRIFFITHS
10/28/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 15, 2011

TO: Mehreen Hai, Regulatory Project Manager
Hyon (KC) Kwon, Clinical Reviewer
Division of Metabolic and Endocrine Products (DMEP)

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

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Jean Mulinde, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

SUBJECT: Evaluation of Clinical Inspections

NDA: 201281

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG: linagliptin and metformin

NME: No

THERAPEUTIC CLASSIFICATION: Standard

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

CONSULTATION REQUEST DATE: April 5, 2011

DIVISION ACTION GOAL DATE: November 18, 2011
PDUFA DATE: November 19, 2011

I. BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 201281 for the use of the combination of linagliptin and metformin as an adjunct to diet and exercise to improve glycemic control in adults with Diabetes Mellitus Type 2 on January 19, 2011. At the time of this submission, linagliptin was considered a new molecular entity and was under review for approval as NDA 201280. The review division had requested inspection of 6 clinical investigator sites and the sponsor for the review of NDA 201280. OSI completed the review of these inspections and no data integrity concerns were identified. A clinical inspection summary for NDA 201280 was signed off in DARRTS on February 11, 2011. Linagliptin (trade name Tradjenta) was approved by the FDA as single therapy for treatment of diabetes mellitus on May 2, 2011. For the current NDA 201281 concerning the combination therapy, the review division requested inspection of the pivotal study Protocol 1218.46 entitled “A Phase III Randomized, Double-blind, Placebo-controlled Parallel Group Study to Compare the Efficacy and Safety of Twice Daily Administration of the Free Combination of Linagliptin 2.5 mg + Metformin 500 mg, or of Linagliptin 2.5 mg + Metformin 1000 mg, With the Individual Components of Metformin (500 mg or 1000 mg, twice daily) and Linagliptin (5 mg, once daily) over 24 Weeks in Drug Naïve or Previously Treated (4 Weeks Washout and 2 Weeks Placebo Run-in) Type 2 Diabetic Patients with Insufficient Glycemic Control” sponsored by Boehringer Ingelheim Pharmaceuticals, Inc.

The primary endpoint was the change in HbA1c from baseline (Visit 3) to Visit 7 (Week 24 at the end of 24 week short term treatment period) determined by a laboratory test performed on blood drawn at the appropriate time points noted above.

Two foreign clinical investigator sites were inspected in support of this application. The sites in India were chosen because India enrolled the largest percentage of subjects (31.5%). The sites chosen are the two sites in India that randomized large numbers of subjects and were not inspected under NDA 201280 for linagliptin.

II. RESULTS (by Site):

Name of Clinical Investigator (CI), or Sponsor & Location	Protocol #/ # Subjects Randomized	Inspection Date	Final Classification
CI: Dr. Vyankatesh Shivane Krishnacharya RHIDEM, 1/15, Rupal Apartments, 3rd Floor, 98, Dadasaheb Phalke Road, Dadar, Mumbai 4000014, India	Protocol 1218.46 30 Subjects	August 9 to 13, 2011	Pending (Preliminary classification NAI)
CI: Dr. Sathyanarayana Srikanta Jnana Sanjeevini, # 2, 1 A Cross, Marenahalli, J. P. Nagar, Phase 2, Bangalore – 560078, India	Protocol 1218.46 24 Subjects	August 22 to 26, 2011	Pending (Preliminary classification VAI)

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. **Dr. Vyankatesh Shivane Krishnacharya**RHIDEM, 1/15, Rupal Apartments, 3rd Floor, 98, Dadasaheb Phalke Road
Dadar, Mumbai 4000014, India

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions concerning data integrity change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** At this site, for Protocol 1218.46, a total of 50 subjects were screened, 33 subjects were enrolled including 30 randomized and 3 open-label. A total of 32 subjects completed the study, and one subject terminated due to lack of efficacy. All 50 subjects' records were reviewed during the inspection.
- b. **General observations/commentary:** No violations were cited and a Form FDA 483 was not issued. There was no evidence of under-reporting of adverse events and the primary endpoint of HbA1C was verified.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. **Dr. Sathyanarayana Srikanta**Jnana Sanjeevini, # 2, 1 A Cross, Marenahalli, J. P. Nagar, Phase 2,
Bangalore – 560078, India

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions concerning data integrity change upon receipt and review of the EIR.

- a. **What was inspected:** At this site, for Protocol 1218.46, a total of 55 subjects were screened, and 28 subjects were enrolled. A total of 21 subjects completed the study, and 4 subjects withdrew due to adverse events including lack of efficacy. A total of 55 subjects' records were reviewed during the inspection.
- b. **General observations/commentary:** The primary efficacy data were verified. There was an adverse event that was reported by the site to the sponsor that was not in the line listings. This was the occurrence of a hematocrit of 31 in Subject 47338 who was then treated with iron replacement. There was no other

evidence of under reporting of adverse events by the clinical investigator or the sponsor. A Form FDA 483, Inspectional Observations was issued for the following:

1. The principal investigator and co-investigators did not adequately review the laboratory reports, clinic notes, and Home Blood Glucose Monitoring (HBGM) logs. For example:
 - i. For Subjects 49425 and 47339, the HBGM log books were not adequately signed off or were not noted in the clinic notes.
 - ii. For Subject 49937, the lab report of a low GFR of 55mL/min/1.73m² was not noted in the clinic records.
 - iii. For Subject 49425, the date of the initiation of Levofloxacin therapy was not correctly stated.
2. There was no assurance that the informed consent process was adequate because there was no documentation that the subject was adequately briefed about the study and provided adequate time to discuss the study with the legally acceptable representative (LAR). For example, the total documented time taken to complete the briefing of the subject and consent process varied from about 25 minutes to 130 minutes in the 55 subjects screened. The briefing of the subjects that took place prior to the informed consent document (ICD) administration day were often not recorded in the subject study file and commented on in the ICD notes. The time taken for various tasks involved in the subject briefing such as explanation of the content of the patient information and the consent form, time allowed for subject's discussions with LAR, and the time for questions and answers were not recorded separately, making it difficult to assess the adequacy of the briefing provided to the subject. Additionally, in the case of illiterate subjects, the language skills of the subject, the LAR, and of the impartial witness were not captured in the ICD notes, and the process of determining the language of consensus was not documented in the ICD notes.

Reviewer note: Item 2 above concerns lack of documentation of adequate informed consent process and is based on review of the Form FDA 483, Inspectional Observations and discussions with the FDA field investigator. A more complete report will be issued upon review of the EIR and exhibits. The protocol required compliance with ICH GCP guidelines and local laws. There were provisions for illiterate subjects. The clinical investigator (CI) responded in a letter dated September 13, 2011 and received by e-mail on September 15, 2011. In the response, the CI noted that the site follows a detailed process consisting of an initial encounter, provision of subject information sheet and informed consent form to subject and family, review encounter and continued discussions, and final encounter and signing of the ICD. There is an additional provision for illiterate subjects. (CI notes that 3 of the 55 subjects in the inspected study were considered illiterate.) The CI acknowledges that the processes for the final encounter were documented, but not the processes prior to this encounter. Because the FDA investigator notes in the Form FDA 483, Inspectional Observations that the consenting process varied from 25 minutes to over 2 hours, it appears that there was some consenting process and the duration was able to be documented. Further assessment of the consenting process cannot be completed until the EIR is reviewed.

3. A serious adverse event that occurred for Subject 49934 was not reported in a timely manner to the sponsor. This SAE occurred in the subject prior to randomization and the subject was not continued in the study. The subject was not randomized and did not receive test article.
- c. **Assessment of data integrity:** The observation on the Form FDA 483, Inspectional Observations concerning the consenting process and the CI response to the observation appear to indicate poor documentation and not a deficiency in the consenting process itself. The exact nature of this violation, if any, and the impact on subject protection will be determined at the time of review of the EIR. The above violations concerning Items 1 and 3 were considered isolated occurrences and unlikely to impact data reliability. The under reporting of a single adverse event by the sponsor appears to be an isolated occurrence. With the exception of issues noted above, the data generated by the site appear to be reliable and may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites that enrolled subjects in Study 1218.46 were inspected in support of this NDA, and based on results of those inspections it appears that data submitted by the Applicant in support of the requested indication should be considered reliable.

Inspection of Dr. Shivane Krishnacharya's site did not note any violations and the preliminary classification for this inspection is No Action Indicated.

Inspection of Dr. Srikanta's site resulted in issuance of a Form FDA 483 for observations concerning deficiencies in review of laboratory reports, clinic notes, and Home Blood Glucose Monitoring (HBGM) logs, informed consent process and reporting of SAE in a subject who was not randomized and did not receive test article. Concerning the informed consent process, this appears to indicate poor documentation and not a deficiency in the consenting process itself. On the Form FDA 483, Inspectional Observations, the FDA field investigator notes that the consenting process for some subjects lasted over 2 hours. The exact nature of this violation, if any, and the impact on subject protection will be determined at the time of review of the EIR. Other violations did not appear to be systemic or widespread in nature, and are unlikely to significantly impact data reliability. Of note, the occurrence of anemia as an adverse event in one subject was reported to the sponsor by the clinical site, but was not reported in adverse event line listings; however, this appears to also have been an isolated finding.

Note: The final classification for both of the clinical investigator inspections are 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 EIRs for these inspections.

{See appended electronic signature page}

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

CONCURRENCE:

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/s/

SUSAN LEIBENHAUT

09/15/2011

LAUREN C IACONO-CONNORS

09/15/2011

JEAN M MULINDE

09/15/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 201281

Name of Drug: Linagliptin and Metformin Hydrochloride Fixed-Dose Combination Tablets

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: The NDA was submitted and received on January 19, 2011, and contained labeling in SPL format. Revised labeling was submitted on August 3, 2011, in response to comments from the Division, but did not contain labeling in SPL format. Therefore, the Word version submitted on August 3, 2011 was used for this review.

Background and Summary Description

This NDA is for linagliptin and metformin hydrochloride fixed-dose combination tablets, indicated for the treatment of Type 2 diabetes mellitus. Linagliptin (tradename: Tradjenta) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) and was approved by the FDA on May 2, 2011, under NDA 201280. Metformin (trade name: Glucophage) is an anti-diabetic drug of the biguanide class and was approved by the FDA on March 3, 1995, under NDA 020357.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement and described in italic blue font.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant, along with other labeling comments identified by the review team, by October 22, 2011. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies, and the resubmitted labeling will be used for further labeling discussions.

Mehreen Hai, Ph.D.	August 24, 2011
Regulatory Project Manager	Date
Julie Marchick, M.P.H.	August 25, 2011
Acting Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- ☐ There is no redundancy of information.
- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- ☐ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- ☐ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “***See full prescribing information for complete boxed warning.***” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- ☐ Removal of a section or subsection should be noted. For example, “Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**

- ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- ☐ Must include a brief, concise summary of critical information and cross-reference to

detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- ☒ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Note: The word “clinical” has been omitted.
- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”

Note: The words “(Patient Information)” have been omitted.

 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

MEHREEN HAI
08/25/2011

MEMORANDUM

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

DATE: August 22, 2011

TO: Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
(DMEP)
Office of Drug Evaluation II

Chandrabhas Sahajwalla, Ph.D.
Director,
Division of Clinical Pharmacology II (DCPII)

FROM: Arindam Dasgupta, Ph.D., Staff Fellow
Division of Bioequivalence and GLP Compliance
(DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader – Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering Linagliptin/Metformin
Hydrochloride Tablets, 2.5 mg/500 mg, 2.5 mg/850
mg, 2.5 mg/1000 mg sponsored by Boehringer
Ingelheim Pharmaceuticals, Inc.

At the request of the Division of Metabolism and Endocrinology Products (DMEP), Office of New Drugs (OND), DBGC audited the clinical and analytical portions of the following bioequivalence (BE) studies.

Study 1288.1: "Bioequivalence of a 2.5 mg linagliptin /1000 mg metformin fixed dose combination tablet compared with single linagliptin 2.5 mg and metformin 1000 mg tablets administered together in healthy male and female volunteers (an

open-label, randomised, single dose, two-way crossover, Phase I trial”

Study 1218.57: “Bioequivalence of two strengths (1000 mg and 500 mg) of two different metformin tablets administered to healthy male and female subjects in an open, randomised, single-dose, two-period crossover, phase I trial”

Audit of the clinical portion of the studies was conducted at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany. Following the inspection of the clinical site (August 1-5, 2011), no Form FDA-483 was issued and there were no significant findings. The audit of the analytical portions of the studies were conducted at

(b) (4)
(b) (4)
(b) (4) Following inspection of the analytical sites Form FDA-483s were issued (**Attachment 1 and 2**). DBGC received the (b) (4) written response to the inspectional findings on August 10, 2011 and August 15, 2011 respectively (**Attachment 3 and 4**)

The 483 observations for studies 1288.1 and 1218.57, (b) (4) response and our evaluations follow:

Analytical Site 1: (b) (4)
(b) (4). (**Linagliptin assay for study 1288.1**)

1. Freeze-thaw stability experiment was not conducted as part of the pre-study method validation. Supporting freeze-thaw stability data generated by the Sponsor was not compared to freshly extracted standard curve.

In their response, (b) (4) acknowledged the observation and indicated that as per (b) (4) SOP, freeze-thaw stability determination was always carried out against freshly prepared calibration curve. Since the inspection, (b) (4)

has conducted freeze/thaw stability experiment against a freshly prepared calibration curve as part of an ongoing clinical study and provided the data in their response. The submitted data showed that linagliptin (BI1356) and CD1750 XX were stable after four freeze thaw cycles when compared against a fresh calibration curve. Hence the above observation should not affect the outcome of the current study.

2. Failure to report all validation experiments containing valid data. For example, data from validation run, Val03r for determination of inter-assay precision and accuracy were discarded and not reported because the data failed to meet acceptance criteria.

In their response, (b) (4) acknowledged the observation and indicated that they would undertake global review of procedures for reporting failed validation data without assignable causes. In addition, (b) (4) also provided tables for precision and accuracy determinations containing the discarded data. Inter-assay precision and accuracy for linagliptin and CD1750 XX was within the acceptable limits when the discarded data were included in the precision accuracy determination.

Hence, the above observation should not affect the outcome of the study.

Analytical Site 2: (b) (4)
(Metformin assay for studies 1288.1 and 1218.57)

1. The analytical method used in an in vivo bioavailability or bioequivalence study was not demonstrated to be accurate because of:

a) Failure to document all aspects of the study conduct. Specifically, the storage location for processed samples 101-149 in runs 4, 5, 6 and 11 in (b) (4) study number CP095285 (BI Trial No: 1288.1) was not documented. As the storage location and conditions can not be confirmed by documentation, the integrity of the processed samples prior to injection into the LC/MS/MS can not be assured.

In their response, (b) (4) acknowledged the observation and indicated that all laboratory personnel would be retrained and reminded about the importance of complete and accurate documentation of laboratory activities in the study notebooks.

Since the inspection (b) (4) also generated new data for processed samples stability at room temperature for 70 hrs. This adequately covered the maximum storage time of processed samples from runs No. 4, 5, 6 and 11. Hence the above observation should not affect the outcome of the studies.

b) Failure to report all validation experiments containing applicable data. Specifically, results of validation experiments conducted to evaluate intra-assay precision and accuracy, long-term stability, and carry-over effect in failed metformin validation run 11 in (b) (4) study #CP055376 were not reported or discussed in the validation report.

In their response, (b) (4) acknowledged the observation and indicated that the method validation SOP would be updated to require all validation experiments to be reported and discussed in the validation Report. In addition, (b) (4) indicated that amendment to the validation report was prepared to report the failed validation run No. 11. In the response (b) (4) indicated that the validation run 11 failed due to improper QC preparation and preparation of internal standard working solution. During the inspection, (b) (4) provided data for long term storage stability for metformin from samples stored for over 9 months at $-24^{\circ}\text{C} \pm 6^{\circ}\text{C}$ which adequately covered the period the study samples were stored. Also precision and accuracy determined for the QCs and calibrators during the analytical runs were acceptable

(b) (4) response is adequate and the above finding is not likely to impact the outcome of the current study.

Conclusion:

Following the above inspections, the Division of Bioequivalence and GLP Compliance recommends that the clinical and analytical data of studies 1288.1 and 1218.57 be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Arindam Dasgupta, Ph.D.

Final Classification:

Clinical

NAI- Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an
der Riss, Germany

Analytical

VAI-  (b) (4)
VAI- 

cc: DARRTS
OND/ODEII/DMEP/Mary Parks/Mehreen Hai
OTS/OCPII/Sahajwala/Manoj Khurana

OC/Ball
OC/DSI/Salewski/Haidar/Dasgupta/Yau/Dejernet
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cc: email
CDER DSI PM TRACK
Draft: AD 08/18/2011
Edits: MKY 8/22/2011
DSI: 6193; 0:\BE\EIRC0VER\201281.boe.lin.met.doc
FACTS:1273004

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/s/

ARINDAM DASGUPTA
08/22/2011

MARTIN K YAU
08/22/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 201281 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: TBD Established/Proper Name: Linagliptin/Metformin Hydrochloride Fixed-Dose Combination Dosage Form: Tablets Strengths: 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: January 19, 2011 Date of Receipt: January 19, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: November 19, 2011		Action Goal Date (if different): November 18, 2011
Filing Date: March 20, 2011		Date of Filing Meeting: March 1, 2011
Chemical Classification (1,2,3 etc.) (original NDAs only) : 1, 4 (Changed to 4 after Linagliptin approval dated May 5, 2011)		
Proposed indication(s)/Proposed change(s): Treatment of Type 2 Diabetes Mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2) N/A
Review Classification: <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>		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted N/A
Resubmission after withdrawal? ☐ N/A		Resubmission after refuse to file? ☐ N/A
Part 3 Combination Product? ☐ N/A <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: N/A	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): IND 70963 and IND 105055				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Standard Review
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ 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: ☒ Not in arrears ☐ In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X		
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)]?			X		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm			X		
If yes, please list below:					
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 (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm			X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
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>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
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:	X			

¹

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

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<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>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			Listed separately in Module 1.1.2
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <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> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	

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

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <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>	X			PeRC scheduled for September 28, 2011
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		

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

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?	X			
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	X			
<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Submitted as an amendment dated April 12, 2011
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ 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>	X			
Is the PI submitted in PLR format? ⁴	X			

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

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

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

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 16, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			Meeting cancelled by sponsor since preliminary responses were adequate
Any Special Protocol Assessments (SPAs)? Date(s): April 13, 2009 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			CMC SPA agreement

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 1, 2011

BLA/NDA/Supp #: NDA 201281

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: Linagliptin-Metformin Fixed Dose Combination

DOSAGE FORM/STRENGTH: Tablets/ 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

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

BACKGROUND: Linagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4) and was studied under IND 70963. The NDA (201280) for linagliptin was submitted on July 2, 2010, and is currently under review. Metformin (Trade name: Glucophage) is an anti-diabetic drug of the biguanide class and was approved by the FDA on March 3, 1995, under NDA 020357. Glucophage is marketed by Bristol-Myers Squibb, which has not given right-of-reference to Boehringer Ingelheim(BI). BI needs to rely on the Glucophage NDA for the safety and effectiveness of metformin, and therefore this NDA for linagliptin-metformin FDC is a 505(b)(2) application.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mehreen Hai	
	CPMS/TL:	Lina AlJuburi	
Cross-Discipline Team Leader (CDTL)	Ilan Irony		
Clinical	Reviewer:	Hyon (KC) Kwon	
	TL:	Ilan Irony	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Manoj Khurana	
	TL:	Sally Choe	
Biostatistics	Reviewer:	Wei Liu	
	TL:	Todd Sahlroot	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	
	TL:	Todd Bourcier	
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Sheldon Markofsky	
	TL:	Suong Tran	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Walter Fava	
	TL:	Carlos Mena-Grillasca	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	

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

FILING MEETING DISCUSSION:

GENERAL	
505(b)(2) filing issues? If yes, list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> - this drug/biologic is not the first in its class	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Although linagliptin was an NME at the date of receipt, it is third-in-class and was approved on

○ <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>	May 2, 2011, while this FDC was under review.
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>																							
Comments:	☐ Review issues for 74-day letter																						
REGULATORY PROJECT MANAGEMENT																							
Signatory Authority: Curt Rosebraugh, M.D. (Office Director) 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Receipt Date: January 19, 2011 60-day Filing Date: Sun, March 20, 2011 74-Day Letter: Sun, April 3, 2011 Standard Review 10-month Goal Date: November 19, 2011 <table> <tr> <td>Filing Mtg:</td> <td>March 1, 2011</td> </tr> <tr> <td>MCR Mtg:</td> <td>June 27, 2011</td> </tr> <tr> <td>Primary reviews complete:</td> <td>September 24, 2011</td> </tr> <tr> <td>Wrap up meeting:</td> <td>September 26, 2011</td> </tr> <tr> <td>PeRC meeting:</td> <td>September 28, 2011</td> </tr> <tr> <td>Secondary reviews complete:</td> <td>October 1, 2011</td> </tr> <tr> <td>Send labeling & PMR/PMCs to sponsor:</td> <td>October 1, 2011</td> </tr> <tr> <td>CDTL review complete:</td> <td>October 8, 2011</td> </tr> <tr> <td>Action package + letter to Div Dir.:</td> <td>October 8, 2011</td> </tr> <tr> <td>Action package + letter to ODE Dir.:</td> <td>October 29, 2011</td> </tr> <tr> <td>Sign Action Letter:</td> <td>November 19, 2011</td> </tr> </table>		Filing Mtg:	March 1, 2011	MCR Mtg:	June 27, 2011	Primary reviews complete:	September 24, 2011	Wrap up meeting:	September 26, 2011	PeRC meeting:	September 28, 2011	Secondary reviews complete:	October 1, 2011	Send labeling & PMR/PMCs to sponsor:	October 1, 2011	CDTL review complete:	October 8, 2011	Action package + letter to Div Dir.:	October 8, 2011	Action package + letter to ODE Dir.:	October 29, 2011	Sign Action Letter:	November 19, 2011
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Action package + letter to Div Dir.:	October 8, 2011																						
Action package + letter to ODE Dir.:	October 29, 2011																						
Sign Action Letter:	November 19, 2011																						
Comments:																							
REGULATORY CONCLUSIONS/DEFICIENCIES																							
☐	The application is unsuitable for filing. Explain why:																						
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Comments provided by Biopharmaceutics reviewer <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review																						

ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

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

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

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/s/

MEHREEN HAI
05/12/2011

DSI CONSULT: Request for Clinical Inspections

Date: April 4, 2011

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

Through: Hyon (KC) Kwon, Pharm.D., MPH/Clinical Reviewer/DMEP
Ilan Irony, M.D./Clinical Team Leader/DMEP

From: Mehreen Hai, Ph.D., Regulatory Project Manager/DMEP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: **NDA 201281**

Applicant/ Applicant contact information (to include phone/email): **Dawn Collette,**

Phone: (203) 798-4268 Email: dawn.collette@boehringer-ingelheim.com

Drug Proprietary Name: **Pending**

NME or Original BLA (Yes/No): **NME**

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): **Treatment of Type 2 diabetes mellitus**

PDUFA: **November 19, 2011**

Action Goal Date: **November 18, 2011**

Inspection Summary Goal Date: **September 16, 2011** (this is one week prior to the due date for primary reviews)

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
Centre # 91004 Dr. Sathyanarayana Srikanta Jnana Sanjeevini, # 2, 1 A Cross, Marenahalli, J. P. Nagar, Phase 2, Bangalore – 560078.	1218.46	55	Treatment of Type 2 Diabetes mellitus
Centre # 91015 Dr. Vyankatesh Shivane Krishnacharya RHIDEM, 1/15, Rupal Apartments, 3rd Floor, 98, Dadasaheb Phalke Road, Dadar, Mumbai – 4000014.	1218.46	50	Treatment of Type 2 Diabetes mellitus

III. Site Selection/Rationale

In Study 1218.46, the pivotal multi-national Phase 3 trial for this NDA, India enrolled the largest number of subjects (31.5%). We are requesting inspections of the two largest Indian sites that randomized the most subjects and were not inspected under NDA 201280 for linagliptin.

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) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

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)

Should you require any additional information, please contact **Mehreen Hai** at **301-796-5073** or **Hyon (KC) Kwon** at **301-796-0190**.

Concurrence: (as needed)

<u>Ilan Irony</u>	Medical Team Leader
<u>Hyon (KC) Kwon</u>	Medical Reviewer
<u>Mary Parks</u>	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**

Page 4-Request for Clinical Inspections

- *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?*

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/s/

MEHREEN HAI
04/04/2011

MARY H PARKS
04/05/2011

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: March 16, 2011

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: (Required for international inspections)
Mary Parks, M.D., Director, Division of Metabolism and Endocrinology Products,
HFD-510

FROM: **Mehreen Hai**, Regulatory Project Manager, Division of Metabolism and Endocrinology
Products, HFD-510

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 201281
Linagliptin-Metformin fixed-dose combination tablets
2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
1288.1	Dr Mario Iovino Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre Dept. of Clinical Research Birkendorfer Strasse 65, Biberach Germany.	(b) (4)
1218.57	Dr Mario Iovino Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre Dept. of Clinical Research Birkendorfer Strasse 65, Biberach Germany.	

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

 X Other (please explain): The pivotal bioequivalence trials and the bioanalysis were conducted outside the US.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **SEPTEMBER 19, 2011**. We intend to issue an action letter on this application by **NOVEMBER 19, 2011**.

Should you require any additional information, please contact **Mehreen Hai, Regulatory Project Manager, 301-796-5073**

Concurrence: (Optional)

Sally Choe	Clinical Pharmacology Team Leader
Manoj Khurana	Clinical Pharmacology Reviewer

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/s/

MEHREEN HAI
03/16/2011

MARY H PARKS
03/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: ER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Mehreen Hai Regulatory Project Manager DMEP, HFD-510, Phone: 796-5073	
REQUEST DATE February 23, 2011	IND NO.	NDA/BLA NO. NDA 201281	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Linagliptin + Metformin FDC tablets	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Treatment of Type II Diabetes	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) Approx September 16, 2011
NAME OF FIRM: Boehringer Ingelheim		PDUFA Date: November 19, 2011	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☒ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE 3TRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	
		REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION	
EDR link to submission: Link to EDR: <u>\\CDSESUB1\EVSPROD\NDA201281\201281.ENX</u>			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: TBD Labeling Meetings: TBD Wrap-Up Meeting: TBD			
STATE OF REQUESTER		Mehreen Hai	
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND	
Reference ID: 2908924			

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MEHREEN HAI
02/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): CDER OSE Consults Margarita Tossa Email: margarita.tossa@fda.hhs.gov WO22 RM 3461, Phone: 796-4053			FROM: Mehreen Hai Regulatory Project Manager DMEP, HFD-510, Phone: 796-5073	
DATE February 15, 2010	IND NO.	NDA NO. 201281	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT January 19, 2011
NAME OF DRUG Linagliptin +Metformin FDC	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Treatment of Type II Diabetes	DESIRED COMPLETION DATE September 16, 2011
NAME OF FIRM: Boehringer Ingelheim				
REASON FOR REQUEST I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☒ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☐ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW OTHER (SPECIFY BELOW):			☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES			☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL			☐ PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: This is a new NDA for a fixed-dose combination of linagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor) and metformin. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Linagliptin is a new molecular entity, and the NDA for the linagliptin monotherapy is also currently under review (NDA 201280). Please review the carton and container labeling and the proposed patient information (located at the end of the package insert). We recognize that OSE will review the PPI once the PI is substantially complete by DMEP. The user fee goal date this NDA is November 19, 2011. Link to EDR: \\CDSESUB1\EVSPROD\NDA201281\201281.ENX Principal Officer: Hyon (KC) Kwon				
SIGNATURE OF REQUESTER Mehreen Hai			METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND	
SIGNATURE OF RECEIVER Reference ID: 2905996			SIGNATURE OF DELIVERER	

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MEHREEN HAI

02/15/2011