CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201281Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201281 SUPPL # HFD # 510

Trade Name Jentadueto

Generic Name Linagliptin and Metformin Hydrochloride Fixed-Dose Combination tablets

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known January 30, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

N/A

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

N/A

d) Did the applicant request exclusivity?

Reference ID: 3079330

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

N/A

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA# N/A

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 201280	Tradjenta (linagliptin) tablets
NDA# 020357	Glucophage (metformin hydrochloride) tablets

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials,

Reference ID: 3079330

such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

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

N/A

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

N/A

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

YES ☐ NO ☒

If yes, explain:

N/A

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

Study 1218.46: A Phase III randomised, 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 glycaemic control

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

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

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

Investigation #1 YES ☐ NO ☒

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

N/A

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

Investigation #1 YES ☐ NO ☒

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

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 1218.46

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

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

Investigation #1		!
		!
IND # N/A	YES ☐	! NO ☐
		! Explain:
		Study 1218.46 was not conducted under an IND.

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

Investigation #1	!
	!
YES ☒	! NO ☐
Explain:	! Explain:
Applicant provided substantial support for Study 1218.46	

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

YES ☐ NO ☒

If yes, explain:
N/A

==========

Reference ID: 3079330

Name of person completing form: Mehreen Hai, Ph.D.
Title: Regulatory Project Manager
Date: January 30, 2012

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Acting Clinical Team Leader

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

MEHREEN HAI
01/30/2012

JEAN-MARC P GUETTIER
01/30/2012

Hai, Mehreen

From: Greeley, George
nt: Thursday, October 13, 2011 8:16 AM
: Hai, Mehreen
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Parks, Mary H
Subject: NDA 201-281 Linagliptin+Metformin

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Mehreen,

This email serves as confirmation of the review for Linagliptin+Metformin conducted by the PeRC PREA Subcommittee on October 12, 2011.

The Division presented a partial waiver in pediatric patients ages birth to nine years because the disease/condition does not exist in children and a deferral for patients ten through sixteen years because the product is ready for approval in adults for the indication of treatment of type 2 diabetes mellitus.

The PeRC agreed with the Division to grant a partial waiver and deferral for the fixed-dose combination product.

The pediatric record is attached for Linagliptin+Metformin.



1_Pediatric_Record .pdf (66 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov
Please consider the environment before printing this e-mail.

2 pages has been withheld in full as B(4) CCI/TS immediately following this page

DEBARTMENT CERTIFICATION

Certification Requirement Section 306(k)(l) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature: Joanne Palmisano

Name of Applicant: Joanne Palmisano, M.D., F.A.C.P.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 7 January 2011

Mailing Address: Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

From: Hai, Mehreen
To: "dawn.collette@boehringer-ingelheim.com"
Subject: RE: NDA 201281 resubmission (linagliptin-metformin FDC)
Date: Monday, January 30, 2012 11:33:00 AM

Hi Dawn,
I received the package insert and the patient information for the linagliptin-metformin NDA that you emailed to me on Friday, January 27, 2012. We accept your revisions included in this labeling.

Thank you,

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

From: dawn.collette@boehringer-ingelheim.com [mailto:dawn.collette@boehringer-ingelheim.com]
Sent: Friday, January 27, 2012 9:42 AM
To: Hai, Mehreen
Cc: dawn.collette@boehringer-ingelheim.com
Subject: RE: NDA 201281 resubmission

Dear Mehreen,
Find attached a word document of the updated, proposed draft linagliptin-metformin package insert and patient information. BI has agreed to all the recent FDA edits.

Changes in the attached version include:

- Revised copyright to trademark symbol in JENTADUETO tradename
- (b) (4) replaced with www.jentadueto.com in the patient information section
- Minor formatting, typographical and grammatical changes

Thank You,
Dawn

Drug Regulatory Affairs
Boehringer Ingelheim
Phone:203 798 4268
Mobile: (b) (6)
Fax: 203 837 4268

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, January 25, 2012 11:30 AM

To: Collette,Dawn (DRA) BIP-US-R
Subject: RE: NDA 201281 resubmission

Hello Dawn,
Please find attached our edits/comments on the package insert and patient information that you emailed me yesterday for the linagliptin-metformin NDA. If you agree with the edits we have made, and have no further edits of your own, please clean up the document and email it back to me. Otherwise, if you have further edits, please let me know when you will be able to send us those edits.

Thanks!

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

From: dawn.collette@boehringer-ingelheim.com [mailto:dawn.collette@boehringer-ingelheim.com]
Sent: Tuesday, January 24, 2012 1:44 PM
To: Hai, Mehreen
Cc: dawn.collette@boehringer-ingelheim.com
Subject: RE: NDA 201281 resubmission

Dear Mehreen,
Find attached a word document of the updated, proposed draft linagliptin-metformin package insert and patient information. All FDA edits that BI has agreed to have been accepted and are no longer visible in the document. The remaining edits and comments reflect BI responses related to FDA prior comments. Additional BI editorial changes are also included in this version.

Please do not hesitate to contact me if you have any questions or comments concerning this submission.

Thank You,
Dawn

Drug Regulatory Affairs
Boehringer Ingelheim
Phone:203 798 4268
Mobile: (b) (6)
Fax: 203 837 4268

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, January 18, 2012 4:15 PM
To: Collette,Dawn (DRA) BIP-US-R
Subject: RE: NDA 201281 resubmission

Hi Dawn,
Please find attached our edits/comments on the package insert and patient information that you submitted in the November 30, 2011 resubmission of the linagliptin-metformin NDA. We have no further comments on the carton and container labels.

Please let me know when you expect to respond to these comments.
THanks!

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

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/s/

MEHREEN HAI
01/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road/P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs

Dear Ms. Collette:

Please refer to your New Drug Application (NDA) dated January 19, 2011, received January 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linagliptin and Metformin Hydrochloride Tablets, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg.

Please also refer to your complete Class 2 resubmission to this NDA, dated and received November 30, 2011. We also refer to:

- Your initial proprietary name submission, dated November 1, 2011, for the proposed proprietary name Jentadueto;
- Our initial correspondence dated November 9, 2011, finding this proposed proprietary name conditionally acceptable;
- Your January 17, 2012, correspondence, received January 17, 2012, requesting re-review of your proposed proprietary name, Jentadueto.

We have completed our re-review of the proposed proprietary name, Jentadueto, and have concluded that it is acceptable

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

If **any** of the proposed product characteristics as stated in your January 17, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
01/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281

ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd/ P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Collette:

We acknowledge receipt on November 30, 2011, of your November 30, 2011 resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for linagliptin and metformin hydrochloride tablets (2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg).

We consider this a complete, class 1 response to our action letter dated November 16, 2011. Therefore, the user fee goal date is **January 30, 2012**.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MEHREEN HAI
12/22/2011

From: Hai, Mehreen
To: "dawn.collette@boehringer-ingelheim.com";
Subject: PI for NDA 201281
Date: Tuesday, November 22, 2011 11:37:25 AM
Attachments: Lina-Met proposed label-FDA edits-21Nov2011.doc

Hi Dawn,
Please find attached our edits/comments on the package insert (PI) that you submitted on November 3, 2011 for the linagliptin-metformin NDA. We recommend that you submit the PI with your further revisions/comments when you re-submit this NDA. We also recommend that you include the revised PPI (patient information) that you emailed me on November 10, 2011 in the NDA re-submission. We will re-start labeling negotiations once the NDA re-submission has been received.

Hope that's clear. If not, please let me know.

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

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/s/

MEHREEN HAI
11/22/2011

From: Hai, Mehreen
To: "dawn.collette@boehringer-ingelheim.com";
Subject: RE: Action letter for NDA 201281
Date: Tuesday, November 22, 2011 9:13:01 AM

Hi Dawn,
Please see our response below (in blue) to your query.
Let me know if you have any further questions.

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

From: dawn.collette@boehringer-ingelheim.com [mailto:dawn.collette@boehringer-ingelheim.com]
Sent: Thursday, November 17, 2011 4:25 PM
To: Hai, Mehreen
Cc: dawn.collette@boehringer-ingelheim.com
Subject: RE: Action letter for NDA 201281

Dear Mehreen,

We'd appreciate guidance from the Agency as we plan for resubmission of the linagliptin/metformin NDA.

1) We are planning to remove [redacted] (b) (4) as a testing facility, and replace it with other facilities already included in the application. **Does FDA agree that this change fully addresses the deficiencies listed in the Complete Response letter?**

FDA Response: Yes, the proposed deletion of [redacted] (b) (4) **from the NDA would address the deficiency listed in the Complete**

Response letter. However, our action on your resubmission will be based on the GMP-compliance status of all manufacturing and testing sites listed in the resubmission at the time of the action.

2) Since the 4-month safety update (4MSU), there is limited new safety information for linagliptin/metformin fixed dose combination tablets. Outlined below is the current status of the only studies that were ongoing as of the 4MSU. No other studies for linagliptin/ metformin are ongoing at this time.

-- 1218.20, 104-week active controlled study linagliptin vs glimepiride, with metformin background therapy. 4MSU data cut-off was June 30, 2010, and last patient out (LPO) was Dec 21, 2010. The final report is planned to be submitted as a supplement to NDA 201280 for TRADJENTA (linagliptin) tablets in the next weeks.
-- 1218.40, 78-week uncontrolled open-label extension for linagliptin tablets, some patients treated with metformin background therapy. 4MSU data cut-off was Oct 15, 2010, LPO was Dec 29, 2010
-- 1218.52, 54-week double-blind, metformin-controlled extension study of 1218.46 (pivotal factorial design study). 4MSU data cut-off was Oct 15, 2010, LPO was June 16, 2011.

With these new data, no significant changes or findings relevant to the safety profile of linagliptin/metformin fixed dose combination tablets have been identified. Please also note that linagliptin/metformin fixed dose combination tablets are not yet marketed in any country, so no foreign labeling or post-marketing safety information are available.

BIPI is therefore requesting to waive the requirement for a safety update in the resubmission. Does the Division concur?

FDA Response: We cannot waive this requirement and would ask that at time of your resubmission you provide us with an update of new safety information as you have done so in this correspondence. If the status for postmarketing safety data of linagliptin remains unchanged or limited, the Division can determine at that point to what extent a review is necessary.

3) Does the Division agree that the Complete Response, with information outlined above, could be considered a Class 1 resubmission?

FDA Response: In general, a resubmission without new clinical data will be a Class 1 resubmission. However, you are proposing other facilities to replace (b) (4) If inspection of these facilities are required, this will be a Class 2 resubmission. A final determination of the type of resubmission will be made upon receipt of your application.

4) With respect to the facilities inspection of the (b) (4) testing facility, we would appreciate clarification of the following points:

- **FDA's Complete Response Letter states that FDA conducted an inspection at this site for our application. We are aware that FDA performed a general inspection of (b) (4) but not an inspection for our application, i.e., a Preapproval Inspection (PAI).**
- **(b) (4) is listed in FDA's Inspectional Classification Database with a classification "VAI" (Voluntary Action Indicated) Per FDA's PAC-ATLS Guidance, a VAI classification is considered a "Satisfactory Current Good Manufacturing Practice (cGMP) Inspection". We agree to remove (b) (4) from the application (as stated above), but would like to understand how to interpret the VAI classification in FDA's database in the context of FDA's Complete Response Letter.**

FDA Response: FDA's inspectional database does not show the most current GMP status of a specific site. You should communicate with your contract facilities for their current GMP status.

Please do not hesitate to contact me if you have any questions.

Thank You,
Dawn

Drug Regulatory Affairs
Boehringer Ingelheim
Phone:203 798 4268
Mobile: (b) (6)
Fax: 203 837 4268

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, November 16, 2011 1:06 PM
To: Collette,Dawn (DRA) BIP-US-R
Subject: Action letter for NDA 201281

Hi Dawn,
We took action a couple of days early for the linagliptin-metformin NDA 201281- it is a complete response based on deficiencies in the facilities inspections. Please confirm receipt of the attached letter, and let me know if you have any questions. The paper copy should come to you in the mail in a few days.

Thanks!

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

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/s/

MEHREEN HAI
11/22/2011

Hai, Mehreen

From: Wood-Cummings, Terri
Sent: Thursday, November 10, 2011 2:59 PM
To: Hai, Mehreen
Cc: Mena-Grillasca, Carlos; Oleszczuk, Zachary; Tossa, Margarita
Subject: FW: Revised CC labels for NDA 201281 in DARRTS

Subject: RE: NDA 201281 linagliptin-metformin: Response to Container Label Revisions

Hi Mehreen,

DMEPA has reviewed the revised container labels submitted by the Applicant on November 8, 2011. All of DMEPA's recommendations from our October 28, 2011 review (RCM# 2011-353) have been addressed, and the labels are found acceptable.

Please let me know if I can be of further assistance.

Thank you,

Terri Wood-Cummings, M.D.
Medical Officer/Medication Safety Evaluator
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management (OMEPRM)
FDA/CDER/OSE
WO Bldg. 22, Room 4421
Mail Stop, Bldg. 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993
terri.wood-cummings@fda.hhs.gov
301.796.2887 (p)

From: Hai, Mehreen
Sent: Wednesday, November 09, 2011 12:46 PM
To: Tossa, Margarita; Mena-Grillasca, Carlos
Subject: Revised CC labels for NDA 201281 in DARRTS

Hi Rita and Carlos,
BI has submitted carton and container labels for the linagliptin-metformin NDA 201281 (Jentadueto), revised to incorporate the comments we sent them.

The submission is in the EDR dated November 8, 2011 (submission sequence #21, DARRTS SDN 22).

The direct links are:
EDR Location: \\CDSESUB1\EVSPROD\IND070930\070930.enx
Cover Letter: \\CDSESUB1\EVSPROD\NDA201281\0021\m1\us\cover-letter.pdf

Thanks!

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

Reference ID: 3083109

-----Original Message-----
From: asr-dontreply@fda.hhs.gov [mailto:asr-dontreply@fda.hhs.gov]
Sent: Tuesday, November 08, 2011 6:11 PM
To: Hai, Mehreen; CDER-OND-DMEP-EDRNOTIFY; CDER-EDR_ASR_Document_Coordinators; CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; Khalsa, Gurminders J; Livermore, Russell J; Thompson, Douglas L. *; CDER-EDRSTAFF
Subject: Successfully Processed eCTD: nda201281 in DARRTS

Successfully Processed eCTD: nda201281 in DARRTS. Details below:

EDR Location: \\CDSESUB1\EVSPROD\NDA201281\201281.enx

For Document Room Staff Use:
Application Type/Number: nda201281
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 22
eCTD Sequence Number: 0021
Letter Date: 11/08/2011
Stamp Date: 11/8/2011

Receipt Date/Time from Notification: 11-08-2011, 16:16:20
Origination Date/Time from Notification: 11-08-2011, 16:15:31
DOCUMENT ID: 4962743

356H Form: \\CDSESUB1\EVSPROD\NDA201281\0021\m1\us\356h.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA201281\0021\m1\us\cover-letter.pdf

3397 Form: NOT FOUND

3674 Form: NOT FOUND

For EDR Staff Use:
The submission has already been processed. The following information is provided if verification is required. No additional action is required on your part

EDR Location: \\CDSESUB1\EVSPROD\NDA201281\0021
Submission Size: 6745511
Gateway Location: \\chdc9681\cderesub\inbound\ectd\ci1320786925176.579606@llnap12_te

Copy to EDR Status: Good-1

For CDER Project Manager Use:
The following submission received through the Electronic Submission Gateway has been processed using the following information. This information will be updated once Document Room personnel have been able to verify the content of the submission.

Application Type/Number: nda201281
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 22
eCTD Sequence Number: 0021
Letter Date: 11/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road/P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs

Dear Ms. Collette:

Please refer to your New Drug Application (NDA) dated January 19, 2011, received January 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linagliptin and Metformin Hydrochloride Tablets, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg.

We also refer to your November 1, 2011, correspondence, received November 1, 2011, requesting review of your proposed proprietary name, Jentadueto. We have completed our review of Jentadueto and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your November 1, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
11/09/2011

From:	Hai, Mehreen
To:	"dawn.collette@boehringer-ingelheim.com";
Subject:	Patient labeling for NDA 201281
Date:	Tuesday, November 08, 2011 3:45:14 PM
Attachments:	Lina-Met PPI - FDA edits - 8Nov2011.doc

Hi Dawn,
Please find attached our comments on the patient labeling for the linagliptin-metformin NDA.
Let me know if you have any questions.

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

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

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/s/

MEHREEN HAI
11/08/2011

From:	Hai, Mehreen
To:	"dawn.collette@boehringer-ingelheim.com";
Subject:	Container labels for NDA 201281
Date:	Monday, October 31, 2011 12:14:37 PM
Attachments:	Container Labels.pdf

Hi Dawn,
Please find attached our comments on the container labels for the linagliptin-metformin NDA.
Let me know if you have any questions.

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

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 [redacted (b) (4)] This statement could be confusing to pharmacists [redacted (b) (4)]

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

1. Delete the statement [redacted (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 [redacted (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.

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/s/

MEHREEN HAI
11/01/2011

From:	Hai, Mehreen
To:	"dawn.collette@boehringer-ingelheim.com";
Subject:	Information request for NDA 201281
Date:	Monday, October 31, 2011 11:41:51 AM

Hello Dawn,
We have the following information request for the linagliptin-metformin NDA, specifically with regards to hypoglycemia and pregnancy outcome:

We acknowledge there is a relationship between hypoglycemia and fetal outcome in rats (i.e., conclusion (b) in your rationale document, shown below). However, we have not been able to establish a causal relationship between the metformin-induced glucose lowering and the fetal malformations in your embryofetal studies in Wistar Han rats. Please submit any additional data or literature justification from rat studies (preferably the Wistar Han strain) that the degree of glucose lowering seen in your embryofetal rat studies is sufficient to cause the observed fetal malformations.

> **b) Involvement of dysglycemia in the observed fetal morphological changes in our teratogenicity studies. Such an exaggerated pharmacological effect leading to significant hypoglycemia, as seen in the healthy non-diabetic animals, should not be relevant for patients since metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) as noted in the approved Glucophage label.**

Thank you,

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

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/s/

MEHREEN HAI
10/31/2011

From:	Hai, Mehreen
To:	"dawn.collette@boehringer-ingelheim.com";
Subject:	NDA 201281 (linagliptin-metformin FDC) labeling edits
Date:	Thursday, October 20, 2011 11:22:15 AM
Attachments:	Lina-Met proposed label-FDA edits-20Oct2011.doc

Hello Dawn,

Please find attached the linagliptin/metformin FDC package insert, with our edits and comments.

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

Please let me know when we can expect to receive your response.

We will also provide comments on the patient package insert and the carton and container labels within the next couple of weeks.

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

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

Fax: 301-796-9712

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

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/s/

MEHREEN HAI
10/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Collette:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for linagliptin and metformin tablets (2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg).

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

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

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

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

From: Hai, Mehreen
To: "dawn.collette@boehringer-ingelheim.com";
Subject: Information request for NDA 201281
Date: Wednesday, September 07, 2011 11:21:10 AM

Hi Dawn,
We have the following information request for NDA 201281 (linagliptin-metformin FDC):

In Section 8.1.2 of the Toxicology Written Summary (Module 2.6.6), the summary discusses qualification of the degradation product (b) (4) There is a reference to the 13-week rat combination toxicity study (Doc. No. U10-1492) stating, "In this study, (b) (4) was spiked to linagliptin at a concentration of (b) (4) (p. 21 of 33). The applicant goes on to calculate "a safety margin to human use of (b) (4) for (b) (4) presumably based on the reported (b) (4) concentration in the administered NOAEL dose.

We cannot locate any information in the final study report documenting levels of (b) (4) or any spiking of linagliptin drug substance. It is possible that the lot of linagliptin used, Batch PR4AZU00546A1, was previously spiked with the (b) (4) degradation product but if so, no reference to that effect was provided. Please clarify where the information referred to in the Toxicology Written Summary comes from and include documentation that confirms the concentration of (b) (4) in the linagliptin used to dose the rats.

Thank you,

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

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/s/

MEHREEN HAI
09/07/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201281

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs

Dear Ms. Collette:

Please refer to your New Drug Application (NDA) dated January 19, 2011, received January 19, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linagliptin and Metformin Hydrochloride Tablets, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg.

We also refer to your April 12, 2011, correspondence, received April 12, 2011, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reason.

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name, (b) (4) in your submission dated April 12, 2011. We request you consider the risks identified above for this alternate name as well and also consider issues that may arise from the use of the (b) (4) (b) (4) If you choose to submit this alternate name for review, provide supporting data that addresses the risks identified above. The review of this alternate name will not be initiated until the new submission is received.

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

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
07/11/2011

From:	Hai, Mehreen
To:	"dawn.collette@boehringer-ingelheim.com";
Subject:	Label for Linagliptin-Metformin
Date:	Friday, July 08, 2011 1:06:34 PM

Hi Dawn,
It came to our attention recently that in the package insert that you have submitted for the linagliptin-metformin NDA (201281), you have referenced the label for Glumetza. This is for Section 13.1 of the linagliptin-metformin label (Carcinogenesis, Mutagenesis, Impairment of Fertility). If you want to include information from the Glumetza label, you will need to submit the relevant Patent Certification, in accordance with 21 CFR 314.50(i).

Thanks!

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

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/s/

MEHREEN HAI
07/08/2011

From: Hai, Mehreen
To: "dawn.collette@boehringer-ingelheim.com";
Subject: RE: NDA 201281 - Linagliptin/Metformin FDC
Date: Wednesday, June 29, 2011 11:27:31 AM

Hi Dawn,
In our 74-day letter, we told you that we plan to communicate proposed labeling and any PMRs by October 1, 2011. Since linagliptin was approved, our internal categorization of the linagliptin-metformin FDC NDA has changed (it is now a combination of two approved products), and therefore, our internal review timelines have changed too. Instead of sending you labeling and PMRs by October 1, we will send them to you by October 22.

Please let me know if you have any questions.

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

From: dawn.collette@boehringer-ingelheim.com [mailto:dawn.collette@boehringer-ingelheim.com]
Sent: Thursday, March 31, 2011 12:12 PM
To: Hai, Mehreen
Subject: RE: NDA 201281 - Linagliptin/Metformin FDC

Thank you Mehreen

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Thursday, March 31, 2011 12:08 PM
To: Collette,Dawn (DRA) BIP-US-R
Subject: RE: NDA 201281 - Linagliptin/Metformin FDC

Hi Dawn,
Please find attached the 74-day letter for NDA 201281 (linagliptin-metformin FDC).

The paper copy should come to you in a few days.
Thanks!

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

From: dawn.collette@boehringer-ingelheim.com [mailto:dawn.collette@boehringer-ingelheim.com]
Sent: Wednesday, March 23, 2011 2:34 PM
To: Hai, Mehreen
Subject: NDA 201281 - Linagliptin/Metformin FDC

Dear Dr. Hai,

It has been approximately 2 months since Boehringer Ingelheim Pharmaceuticals Incorporated submitted the Linagliptin/Metformin FDC NDA (201281). On January 31st BIPI received an NDA acknowledgment letter indicating March 20, 2011 as a possible filing date for this NDA. Can you share with me the status of this NDA (201281)?

If you have any questions or comments concerning this submission, please do not hesitate to call me. My phone number is (203) 798-4268.

Thank You,
Dawn

Drug Regulatory Affairs
Boehringer Ingelheim
Phone:203 798 4268

Mobile: (b) (6)

Fax: 203 837 4268

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/s/

MEHREEN HAI
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd., P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Collette:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (linagliptin and metformin) Tablets 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product

1. Aside from your (b) (4) procedure for (b) (4), you should indicate and describe, if appropriate, any other (b) (4) of the drug product that may be carried out.

2. Establish an in-process control for the (b) (4) or justify why such a control is not needed, since it was indicated in your process development section that if the (b) (4)

3. Provide protocols for the qualification of any future reference standards for linagliptin related impurities (b) (4) metformin HCl, metformin related impurities (b) (4) or the arginine reference standard. For these reference standards, you should give the source (if purchased) and whether or not the reference standard is obtained from a pharmacopieial institution such as the USP. All of the protocols should state the specifications (analytical methods, and acceptance criteria) that these materials should meet to qualify as reference standards and how often these standards are requalified. In addition, provide for those standards prepared "in-house" by Boehringer Ingelheim, a brief description their syntheses and purifications.

4. Provide Engineering drawings for all of the bottles and closures that you plan to employ for your linagliptin/metformin HCl tablets. The drawings should include the dimensions of these components, as appropriate; and you should provide the allowable tolerances (acceptance criteria) for these dimensions.

5. Provide the acceptance criteria for the Fill Weights for the various desiccant packets that you plan to use in the container/closure systems that you propose to market your tablets.

Labeling

1. Section 1.14.1.1 in the labeling section of the electronic submission indicates that there are both draft carton and container labels in the submission. However, only container (bottle) labels were provided. You should explain this discrepancy and provide the carton labels, if appropriate.

2. Since the product needs to be protected from high humidity, your immediate container labels should contain a brief statement about the need to keep the desiccant packet in the bottle after opening.

3. Provide up-dated carton and immediate container labels with your newly proposed proprietary name for linagliptin/metformin HCl tablets.

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

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief, Branch VII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
06/15/2011

From: Hai, Mehreen
To: "dawn.collette@boehringer-ingelheim.com";
Subject: RE: NDA 201281 linagliptin / metformin hydrochloride tablets dissolution data
Date: Wednesday, May 18, 2011 2:44:54 PM

Hi Dawn,
In response to your query below, Option (a) (**Submit a response which includes a summary of the information from the 1288.6 clinical trial report**) is acceptable.

Thanks!

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

From: dawn.collette@boehringer-ingelheim.com [mailto:dawn.collette@boehringer-ingelheim.com]
Sent: Wednesday, May 18, 2011 6:43 AM
To: Hai, Mehreen
Cc: dawn.collette@boehringer-ingelheim.com
Subject: NDA 201281 linagliptin / metformin hydrochloride tablets dissolution data

Dear Mehreen,

The 74-day letter for NDA 201281 (linagliptin / metformin hydrochloride tablets) dated March 31, 2011 notes the below potential review issue:

The provided dissolution data do not support your proposed dissolution specification of

Q = (b) (4) *at 30 minutes. Therefore, we request that the dissolution specification be*

changed to no less than (b) (4) *of the labeled amount of the drug substance dissolved in 20*

minutes.

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) appreciates the agency's preliminary notice and would like to propose a new dissolution specification (i.e., Q = (b) (4) at 30 minutes). BI is of the opinion that the results of a recently completed study (1288.6) titled "Relative bioavailability of two different batches of a 2.5 mg linagliptin / 1000 mg metformin fixed dose combination tablet (FDC) in healthy male and female volunteers (an open-label, randomized, single dose, two-way crossover, Phase I trial)" support the new proposed dissolution specification. The clinical trial report for this study was not available at the time the original NDA (201281) was submitted, yet is now available.

BIPI would like to respond to the issue noted in the 74-day letter yet we do not wish to disrupt the review timelines. Therefore we propose two options:

a) Submit a response which includes a summary of the information from the 1288.6 clinical trial report

b) Submit the full clinical trial report for study 1288.6 to NDA 201281 as part of the response

We respectfully request your preference.

If you have any questions or comments concerning this issue, please do not hesitate to call me. My phone number is (203) 798-4268.

Thank You,
Dawn

Drug Regulatory Affairs
Boehringer Ingelheim
Phone:203 798 4268

Mobile: (b) (6)
Fax: 203 837 4268

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/s/

MEHREEN HAI
05/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281 **PREA WAIVER DENIED**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd/ P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Collette:

Please refer to your submission dated January 19, 2011, requesting a (b) (4) waiver under 505B(a)(4) of the Federal Food, Drug, and Cosmetic Act for pediatric studies for linagliptin and metformin tablets (2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg) for the treatment of patients with type 2 diabetes mellitus.

We have reviewed your submission and do not agree that a (b) (4) waiver of pediatric studies in patients ages 0 to 16 is justified for linagliptin and metformin tablets (2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg) for the treatment of patients with type 2 diabetes mellitus.

A (b) (4) waiver for pediatric studies for this application is denied at this time. Please submit your pediatric drug development plan by **June 13, 2011**. Your pediatric drug development plan must address treatment of pediatric patients with type 2 diabetes mellitus. We will consider a partial waiver of the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impractical. We also will consider a partial deferral of the pediatric study for ages 10 to 16 years (inclusive).

A pediatric drug development plan (or pediatric plan) is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetic/pharmacodynamics including assessment of swallowability, safety and efficacy). The pediatric plan must contain a timeline for the completion of these studies, i.e., the dates (M/D/Y) of (1) protocol submission (2) study completion and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MARY H PARKS
05/12/2011

From:	Hai, Mehreen
To:	"dawn.collette@boehringer-ingelheim.com";
Subject:	Information request for NDA 201281
Date:	Friday, April 08, 2011 3:03:32 PM
Attachments:	IR NDA 201281.pdf

Hi Dawn,
Please find attached an information request for NDA 201281 (linagliptin + metformin). Please confirm that you were able to open and read the attachment.

Thanks!

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

I. Request for specific protocol information and site level and subject level data:

For 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" please provide the information below for the following two sites:

1. Dr. Sathyanarayana Srikanta site 91004
2. Dr. Vyankatesh Shivane Krishnacharya site 91015

Please provide the information listed below:

A. For each investigator, please provide telephone number, fax number and e-mail address.

B. Please provide an electronic copy of the protocol and blank eCRF.

C. Please provide the following site-specific individual subject data ("line") listings by subject number, from the datasets.

    1. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
    2. Subject listing for treatment assignment (randomization)
    3. Subject listing of drop-outs and subjects that discontinued with date and reason
    4. Evaluable subjects/ non-evaluable subjects and reason not evaluable
    5. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
    6. By subject listing, of AEs, SAEs, deaths and dates, including events qualifying for adjudication and hypoglycemic events
    7. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
    8. By subject listing of the primary endpoint efficacy parameters HbA1C. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
    9. By subject listing of exposure to randomized study drug
    10. By subject listing of concomitant medications including rescue medications (antidiabetic medications)
    11. By subject listing, of laboratory tests performed for safety monitoring

II. Request for information concerning request for waiver from the requirements outlined in 21 CFR 312.120

In your request for a waiver from the requirements outlined in 21 CFR 312.120 submitted in NDA 201281, you state that not all technical requirements of the new rule as outlined in 21CFR 312.120(b) have been met. Please state the requirements that have and have not been met.

Reference ID: 2930684

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/s/

MEHREEN HAI
04/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281

FILING COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd/ P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Collette:

Please refer to your New Drug Application (NDA) dated and received January 19, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for linagliptin and metformin tablets (2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg).

We also refer to your submissions dated February 7 and March 11, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **November 19, 2011**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 1, 2011.

During our filing review of your application, we identified the following potential review issues:

The provided dissolution data do not support your proposed dissolution specification of Q = (b) (4) at 30 minutes. Therefore, we request that the dissolution specification be changed to no less than (b) (4) of the labeled amount of the drug substance dissolved in 20 minutes.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a (b) (4) waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b) (4) waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MARY H PARKS
03/31/2011

From:	Hai, Mehreen
To:	dawn.collette@boehringer-ingelheim.com;
Subject:	Information request for NDA 201281
Date:	Tuesday, March 08, 2011 3:51:32 PM

Hi Dawn,
We have the following information request for NDA 201281 (Linagliptin-Metformin FDC):
Please provide raw concentration and PK/PD parameter data (preferably as SAS transport files) for all BE/Clin Pharm studies (1288.1, 1288.2, 1288.3, 1288.4, and 1218.57) and the PKPD study (1218.45), for both linagliptin and metformin, as applicable.

• The concentration data-set(s) should at least have the following columns: ID, Analyte Name, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.

• The PK/PD parameter data set(s) should at minimum have the following columns: ID, Trial Number, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence.

Please provide a response as soon as possible.
Thank you!

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

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/s/

MEHREEN HAI
03/08/2011

From: Sharma, Khushboo
Sent: Tuesday, January 25, 2011 9:51 AM
To: 'dawn.collette@boehringer-ingelheim.com'
Subject: Request for NDA 201281

Dear Ms. Collette,

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 201281 received January 19, 2011. We have the following comments and information requests. We request a prompt written response within a week in order to continue our evaluation of your submission:

- **You indicate in section 3.2.P.2 that "A series of design experiments has been performed to investigate and improve the robustness of the manufacturing process." No design space is found in the CMC sections of the NDA. For FDA's review planning purposes, we request a confirmation that you do not intend to propose a design space in the manufacturing process of the product.**

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

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

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

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/s/

KHUSHBOO SHARMA
01/25/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201281

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Dawn Collette
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd/ P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Collette:

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

Name of Drug Product: TRADEAME (linagliptin and metformin tablets) 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg

Date of Application: January 19, 2011

Date of Receipt: January 19, 2011

Our Reference Number: NDA 201281

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 20, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products (DMEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-1211 until February 7. After that date, contact Mehreen Hai, Ph.D, who is the Regulatory Project Manager for this application, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ENID M GALLIERS
01/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 105055

MEETING CANCELLED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Maureen Oakes, Pharm.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Oakes:

Please refer to your Pre-Investigational New Drug Application (PIND) for linagliptin and metformin hydrochloride (HCl) fixed-dose combination (FDC) tablets.

We also refer to your March 16, 2010, email communication requesting cancellation of the Pre-NDA meeting that we scheduled for March 16, 2010, in response to your January 20, 2010 meeting request, because our preliminary meeting comments and our responses to your additional follow-up questions adequately addressed all the questions that you had. Therefore, the March 16, 2010, meeting was cancelled.

Our pre-meeting responses that were sent to you via email on March 12 and 16, 2010, are attached for your reference.

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

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Pre-meeting response to questions in meeting request (emailed on March 12, 2010)
Pre-meeting response to follow-up clarification questions (emailed on March 16, 2010)

FDA PRELIMINARY RESPONSES SENT TO BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., ON FRIDAY, MARCH 12, 2010

APPLICATION: PIND 105055

DRUG PRODUCT: LINAGLIPTIN-METFORMIN FIXED DOSE COMBINATION

MEETING TYPE: TYPE B, PRE-NDA

INDUSTRY MEETING DATE: TUESDAY, MARCH 16, 2010

INDUSTRY MEETING PLACE: FDA, WHITE OAK CAMPUS, BLDG 22

REGULATORY PROJECT MANAGER (RPM): MEHREEN HAI, PH.D.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for MARCH 16, 2010 at 1:00 – 2:00 PM between BOEHRINGER INGELHEIM and the Division of Metabolism and Endocrinology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Reference ID: 3083109

Sponsor's Questions and FDA's Preliminary Responses

Question 1a:

Does the Division concur that this clinical data package is adequate to support an assessment of the efficacy and safety of concomitant administration of linagliptin and metformin for all three intended dose strengths in patients with type 2 diabetes?

FDA Preliminary Response: Yes, it is adequate.

Question 1b:

Does the Division have any comments on the proposed contents of Module 5 or BI's plans to cross-reference reports previously submitted in the linagliptin NDA?

FDA Preliminary Response: The contents and plans to cross-reference are acceptable.

Question 2

Does the Division agree with this approach for handling the results of this patient population in the 1218.46 study?

FDA Preliminary Response: Your plans are acceptable; however, you will need to submit the full datasets for this patient population.

Question 3

Does the Division have any comments regarding the proposed structure and content of the modules 2.7.1 and 2.7.2?

FDA Preliminary Response: Your proposed format for Module 2.7.1 and 2.7.2 seems acceptable. The planned clinical pharmacology studies seems reasonable, however there is lack of details of the study design or synopsis for these trials in order to determine their adequacy. For example, it is not clear what source of metformin reference product will be

Reference ID: 3083109

utilized in these BE trials. It is recommended that you use the US reference listed drug for metformin in these pivotal BE trials.

We remind you that because of the non-linearity of linagliptin pharmacokinetics, the traditional BE assessment and its goal post (80-125%) might not be applicable to the bioequivalence assessment for linagliptin. It is recommended that you also calculate bioequivalence using the dose-scale method as secondary analysis. Please refer to the advice letter for IND 070963, dated May 15, 2009, for details.

Question 4

Does the Division have any comments regarding the proposed structure and content of the SCE for linagliptin/metformin FDC tablets?

FDA Preliminary Response: On page 6 of your Pre-NDA Information Package, you list studies that will be supportive for your NDA application. Study 1218.18 is listed here. However, none of your efficacy groupings includes this study for analysis. Please clarify why Study 1218.18 is not included in any of your efficacy groupings.

Question 5

Does the Division have any comments regarding the proposed structure and content of the SCS?

FDA Preliminary Response: We recommend that you include a section dedicated to cardiovascular safety in your SCS and in your more detailed ISS.

Question 6

Does the Agency have any comments to our overall statistical analysis approach?

FDA Preliminary Response: Your statistical analysis approach is acceptable.

Reference ID: 3083109

Question 7

Does the Agency agree that this approach of addressing the quantitative safety analysis is sufficient, and that an additional stand-alone QSAP is not required?

FDA Preliminary Response: Yes, we agree that an additional stand-alone QSAP is not required.

Question 8

Does the Division agree with this proposal?

FDA Preliminary Response: No, we do not agree. You have listed 1218.6 as a supportive study for this NDA. Please also submit the CRFs from deaths and discontinuations due to adverse events from Study 1218.6.

Question 9

Does this Division concur with this proposal?

FDA Preliminary Response: No, we do not agree. Please also submit the case narratives from deaths and discontinuations due to adverse events from Study 1218.6.

Question 10

Does the Division concur with this proposal?

FDA Preliminary Response: Again, please include datasets from Study 1218.6.

Question 11

Does FDA have any comments to the proposed safety package proposed to be submitted to the 4-month safety update?

FDA Preliminary Response: Please ensure that your NDA is complete at the time of submission. Your 4-month safety update should not include anticipated new safety or efficacy data that you deem necessary for review or approval.

Reference ID: 3083109

Question 12

Does the Division have any further comment on BI's plans for the submission of clinical data to the linagliptin/metformin NDA?

FDA Preliminary Response: We have no further comments at this time.

Question 13

Does the Division have any comments on the proposed contents of Module 4 or to BI's plans for cross-referencing to the linagliptin NDA?

FDA Preliminary Response: The organization of Module 4 appears to be acceptable. Please include summaries and discussion relevant to combination linagliptin + metformin pharmacology and toxicology. We also request that you include links and/or references to the linagliptin monotherapy NDA for any sections that reference data (or are left blank but for which there are relevant data) from the linagliptin NDA.

Please consider the following when preparing the non-clinical sections for NDA submission:

- **Include final study reports of the non-clinical studies. Draft reports will not be accepted.**
- **Histopathology sections should describe individual animal findings in addition to the summary tables, complete with incidence and severity scores.**
- **Summary toxicology tables are best separated by species and accompanied by a listing of drug-related acute, subchronic, and chronic study findings, in-life observations, necropsy findings, and statistical notation where appropriate.**
- **Include a table that lists the drug batches used in non-clinical and clinical studies, including links to impurity profiles. This is particularly important considering your use of different metformin drug substances in your clinical program.**
- **Non-clinical studies in PDF file format are preferred over scanned images of the data.**

Reference ID: 3083109

Question 14

Does the FDA agree that the design and the results of the performed 13-week toxicity study in rats (study no. 09B104) are adequate to support the registration of the linagliptin/metformin FDC in all three dose ratios (2.5 mg linagliptin + 500, 850 or 1000 mg metformin hydrochloride)?

FDA Preliminary Response: The study included appropriate control and treatment groups to assess toxicological effects of combined linagliptin + metformin treatment in rats. Support of the proposed FDC indication will be a review issue.

Question 15 a.

Does the FDA agree that the design of the performed embryofetal reproductive toxicology studies in rats with metformin mono (09B099) and with a linagliptin and metformin combination (09B138) are adequate to support the registration of the fixed dose combination of linagliptin and metformin hydrochloride in all three dose ratios (2.5 mg linagliptin + 500, 850 or 1000 mg metformin hydrochloride)?

FDA Preliminary Response: The studies included appropriate control and treatment groups to assess toxicological effects of combined linagliptin + metformin treatment on embryofetal development in rats. Support of the proposed FDC indication will be a review issue.

Questions 15b.

Does the FDA concur that the toxicological program consisting of a 13-week combination study in rats (09B104), an embryo fetal reproductive toxicology study with metformin mono in rats (09B099) and an embryofetal reproductive combination study in rats (09B138) supported by a full nonclinical safety profile for each of the components is sufficient to support the registration of the fixed dose combination?

FDA Preliminary Response: Nonclinical data from individual drugs and the battery of combination toxicology studies will be sufficient to allow review of nonclinical support for the proposed indication. Support of the proposed FDC indication will be a review issue.

Reference ID: 3083109

Question 16:

Does FDA have any comments to the general organization and/or proposed content to be included in Module 3 of the NDA?

FDA Preliminary Response: Your organization and proposed content for Module 3 appears to be adequate. We remind you to provide the following in the NDA: References to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the drug substance and drug product. We may have additional requests at the time of or after submission of your NDA.

Question 17:

Does the FDA agree with BI's proposed stability data submission strategy for the mail order pharmacy bottle?

FDA Preliminary Response: Your proposed stability package is acceptable. Review of additional stability data will depend on the timeliness of its submission. Data submitted after the Mid-Cycle of review will be reviewed at the discretion of the review team.

Question 18:

Does FDA agree with the number of executed batch records proposed for submission?

FDA Preliminary Response: Yes, we agree that one executed batch record for each fixed dose combination and primary stability batch will be sufficient.

Question 19:

Does the Agency have any comments on BI's proposed approach for linagliptin/metformin FDC tablets in the type 2 pediatric population?

FDA Preliminary Response: Your plan to submit the waiver is acceptable. However, whether or not the waiver will be granted is a review issue that will be decided after filing.

Reference ID: 3083109

Additional CMC comments:

1. **The metformin-related impurity profile in the final linagliptin and metformin hydrochloride fixed-dose combination tablets should be fully characterized in your nonclinical studies. Thus, drug substance impurities in toxicology studies must cover all impurities in the clinical & commercial FDC drug product formulations.**

2. **All manufacturing and testing facilities of the two commercial drug substances (and drug product) should be listed in Form 356h for the fixed-dose-combination (FDC) NDA. Specific links to locations in the linagliptin NDA should be stated in each section of the linagliptin drug substance of the FDC NDA.**

Reference ID: 3083109

FDA RESPONSES SENT TO BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. ON MARCH 16, 2010, **IN LIEU OF FACE-TO-FACE MEETING**

APPLICATION: PIND 105055

DRUG PRODUCT: LINAGLIPTIN-METFORMIN FIXED DOSE COMBINATION

MEETING TYPE: TYPE B, PRE-NDA

INDUSTRY MEETING DATE: MARCH 16, 2010

INDUSTRY MEETING PLACE: FDA, WHITE OAK CAMPUS, BLDG 22

REGULATORY PROJECT MANAGER (RPM): MEHREEN HAI, PH.D.

Please find below your pre-meeting response and questions, sent by email to Mehreen Hai on March 15, 2010, and the FDA's response to your questions in bold italic font (only Questions 3, 4, 5, 11, 16 and Additional CMC comment #2, for which BI has posed questions, are shown below).

Re: Linagliptin-Metformin Fixed Dose Combination (PIND 105055)
Date: March 15, 2010

Boehringer Ingelheim (BI) appreciates the comments of the Division (dated March 12, 2010) to the pre-NDA meeting package for the linagliptin/metformin fixed dose combination (FDC) tablets. We find the remarks and answers of the Division clear and therefore do not feel that a face-to-face meeting is warranted. However, a teleconference is requested if the Agency is unable to address our italicized comments below under questions 3, 4, 5, 11, 16 and "additional CMC comments #2" prior to the scheduled meeting time.

We have highlighted the questions for which we are providing and/or seeking further clarification. Of note, many of the original 19 questions are not addressed in this correspondence as BI has reviewed these and accepts the recommendations of the Division.

Question 3
Does the Division have any comments regarding the proposed structure and content of the modules 2.7.1 and 2.7.2?

FDA Preliminary Response: Your proposed format for Module 2.7.1 and 2.7.2 seems acceptable. The planned clinical pharmacology studies seems reasonable, however there is lack of details of the study design or synopsis for these trials in order to determine their adequacy. For example, it is not clear what source of metformin reference product will utilized in these BE trials. It is recommended that you use the US reference listed drug for metformin in these pivotal BE trials.

We remind you that because of the non-linearity of linagliptin pharmacokinetics, the traditional BE assessment and its goal post (80-125%) might not be applicable to the bioequivalence assessment for linagliptin. It is recommended that you also calculate bioequivalence using the dose-scale method as secondary analysis. Please refer to the advice letter for IND 070963, dated May 15, 2009, for details.

BI response: The European reference product (Glucophage Merck Serono) was used in the pivotal phase III study 1218.46 (500 mg and 1000 mg) and its extension 1218.52 (500 mg, 1000 mg), which was conducted with the free combination of 2.5 mg linagliptin and 500/1000 mg metformin. To bridge this study to the US reference product (Glucophage BMS), a bioequivalence study of the two products (Glucophage BMS and Glucophage Merck Serono) at both dose strengths of 500 mg and 1000 mg was performed [study 1218.57 (report synopsis attached)]. Results of this study demonstrate bioequivalence between the US and European commercial products.

In addition, BI conducted studies 1288.1, 1288.2 and 1288.3 to demonstrate bioequivalence between the single entity tablets used in phase III Study 1218.46 and the final FDC tablet formulations proposed for commercialization in the US. All these BE

studies were conducted according to a randomized, two way-crossover, fasted, single dose design in accordance with current regulatory guidelines. The protocol synopses of the 1288.1, 1288.2 and 1288.3 studies are attached.

Does the Division have any further comments on BI's approach regarding the reference product or require further clarification on the details of the studies described above?

FDA Response: We do not require further clarification on the details of the BE studies. This will be a review issue.

Question 4

A mock version of the Module 2.7.3 Summary of Clinical Efficacy (SCE) to be provided in the linagliptin/metformin NDA is included in Appendix 6. The SCE mock document presents the proposed approach for presenting efficacy data, including methodology, table shells, section headings and groupings of clinical studies.

Does the Division have any comments regarding the proposed structure and content of the SCE for linagliptin/metformin FDC tablets?

FDA Preliminary Response: On page 6 of your Pre-NDA Information Package, you list studies that will be supportive for your NDA application. Study 1218.18 is listed here. However, none of your efficacy groupings includes this study for analysis. Please clarify why Study 1218.18 is not included in any of your efficacy groupings.

BI response: The objective of study 1218.18 was to investigate the efficacy and safety of linagliptin 5 mg versus placebo administered for 24 weeks as add-on to a background therapy of metformin in combination with sulphonylurea to patients with type 2 diabetes mellitus and insufficient glycaemic control. Based on the design of the 1218.18 study, it was not considered an essential part for investigation of efficacy of the NDA submission of linagliptin/metformin. Cross-reference will be made to the linagliptin NDA (ISE) where this study will be included for efficacy analysis. Furthermore the linagliptin/metformin NDA will include the full CTR of the 1218.18 study.

Does the Division concur with this approach?

FDA Response: Yes, we concur.

Question 5

A mock version of the Module 2.7.4 Summary of Clinical Safety (SCS) to be provided in the linagliptin/metformin NDA is included in Appendix 7. The SCS mock document presents the proposed approach for presenting safety data, including methodology, table shells, section headings and groupings of clinical studies.

Does the Division have any comments regarding the proposed structure and content of the SCS?

FDA Preliminary Response: We recommend that you include a section dedicated to cardiovascular safety in your SCS and in your more detailed ISS.

BI response: Information contained within the linagliptin NDA will serve as the basis for establishing the cardiovascular (CV) profile of linagliptin. The linagliptin/metformin FDC NDA will cross reference the linagliptin NDA for this information.

Does the Division concur with this approach?

FDA Response: Yes, we concur.

Question 11

Does FDA have any comments to the proposed safety package proposed to be submitted to the 4-month safety update?

FDA Preliminary Response: Please ensure that your NDA is complete at the time of submission. Your 4-month safety update should not include anticipated new safety or efficacy data that you deem necessary for review or approval.

BI response: BI appreciates the comments of the Division and understands that the 4-month safety update is not intended to present new efficacy information for consideration with the original NDA application and that the Agency is not obligated to review such information. BI would like to confirm that the 4-month safety update will include a summary on new safety data from studies not yet included at time of the NDA submission of linagliptin/metformin.

Does the Division concur with this approach?

FDA Response: Yes, we concur.

Question 16:

Does FDA have any comments to the general organization and/or proposed content to be included in Module 3 of the NDA?

FDA Preliminary Response: Your organization and proposed content for Module 3 appears to be adequate. We remind you to provide the following in the NDA: References to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the drug substance and drug product. We may have additional requests at the time of or after submission of your NDA.

BI Response: We acknowledge FDA's agreement on the proposed organization and content of Module 3. However, we are not sure if our revised question 16 (Amendment to Pre-NDA Meeting Information Package, dated March 8, 2010) was clearly received by the Division. Therefore, BI would like to confirm that the Division does agree that there will be no drug substance section (3.2.S) for linagliptin drug substance in the linagliptin/metformin FDC NDA and that there will be one drug substance section (3.2.S) only for metformin drug substance.

Does the Division agree with this approach?

FDA Response: Yes, we agree with your approach. Hyperlinks will not be required as they may become out-of-date as the linagliptin NDA is amended. Your linagliptin/metformin FDC NDA should still reference the drug substance section in the linagliptin NDA.

Additional CMC comments:

2. All manufacturing and testing facilities of the two commercial drug substances (and drug product) should be listed in Form 356h for the fixed-dose-combination (FDC) NDA. Specific links to locations in the linagliptin NDA should be stated in each section of the linagliptin drug substance of the FDC NDA.

BI Response:. Please clarify what is meant by "Specific links to locations in the linagliptin NDA should be stated in each section of the linagliptin drug substance of the FDC NDA". Is the proposal is to create hyperlinks from the FDC NDA to the Linagliptin NDA? If this is the proposal, we have concerns regarding the feasibility of this request. We would like to reiterate our initial proposal that there will be no drug substance section (3.2.S) for the linagliptin drug substance in the linagliptin/metformin FDC NDA and that there will be one drug substance section (3.2.S) only for metformin drug substance (please see our comment to Question 16).

Does the Division agree with this approach?

FDA Response: Please refer to the response to Question 16 above.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105055	GI-1	BOEHRINGER INGELHEIM	BI 1356 + metformin HCl FDC Tablets

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

/s/

MEHREEN HAI
05/04/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **201281** BLA # **N/A**	NDA Supplement # **N/A** BLA STN # **N/A**	If NDA, Efficacy Supplement Type: **N/A**
Proprietary Name: **Jentadueto** Established/Proper Name: **Linagliptin and Metformin Fixed-Dose Combination 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg** Dosage Form: **Tablets**		Applicant: **Boehringer Ingelheim** Agent for Applicant (if applicable): **N/A**
RPM: **Mehreen Hai**		Division: **Metabolism and Endocrinology Products (DMEP)**

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

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

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

Glucophage (metformin hydrochloride) tablets (NDA 020357)

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

This product is a fixed-dose combination of linagliptin and Glucophage

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

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

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

☒ No changes ☐ Updated Date of check: **1-30-12**

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

❖ Actions	
• Proposed action • User Fee Goal Date is **January 30, 2012**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ CR **November 16, 2011**

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

Reference ID: 3083109

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

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

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

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

Comments: **None**

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

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

Reference ID: 3083109

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

Reference ID: 3083109

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

Reference ID: 3083109

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	**2-1-12**
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	**CR – November 16, 2011** **AP – January 30, 2012**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	**1-30-12**
• Original applicant-proposed labeling	**1-19-11 and 8-3-11**
• Example of class labeling, if applicable	**Tradjenta (linagliptin)** **Glucophage (metformin HCl)** **Janumet (sitagliptin and metformin FDC**

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

Reference ID: 3083109

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	**1-30-12**
• Original applicant-proposed labeling	**1-19-11 and 8-3-11**
• Example of class labeling, if applicable	**Tradjenta (linagliptin)** **Janumet (sitagliptin and metformin FDC)**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	**11-8-11**
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 **7-11-11, 11-9-11, 1-26-12** **7-11-11, 11-9-11, 1-26-12**
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM **8-25-11 (PLR review)** ☒ DMEPA **10-31-11** ☒ DRISK **10-28-11** ☒ DDMAC **11-3-11** ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	**5-12-11 (RPM Filing review)** **1-25-12** **1-25-12**
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC **10/12/11** If PeRC review not necessary, explain: • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

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

Reference ID: 3083109

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	**1-24-11, 1-25-11, 3-8-11, 3-31-11, 4-8-11, 5-12-11, 5-18-11, 6-15-11, 6-29-11, 7-8-11, 9-7-11, 9-7-11, 10-20-11, 10-31-11, 11-1-11, 11-8-11, 11-22-11, 11-22-11, 12-22-11, 1-30-12**
❖ Internal memoranda, telecons, etc.	☒ None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	**3-16-10**
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	**11-8-11, 1-26-12**
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ None
• Clinical review(s) *(indicate date for each review)*	**3-3-11 (filing), 10-14-11**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**Pages 12 of Clinical review**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

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

Reference ID: 3083109

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	**9-15-11, 11-21-11, 12-23-11**
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	**3-8-11 (filing), 10-17-11**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	**5-3-11 (filing), 10-11-11**
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	**8-22-11**
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**3-2-11 (filing), 10-4-11, 11-16-11, 1-26-12**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	**CMC: 3-1-11 (filing), 6-15-11, 9-26-11, 11-8-11, 12-22-11 BioPharm: 3-14-11 (filing), 9-19-11**
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Reference ID: 3083109

Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**Page 138 of Chemistry review**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: **12-20-11** ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: **N/A** ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

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

Reference ID: 3083109

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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