CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208026

Trade Name Jentadueto XR

Generic Name (linagliptin and metformin hydrochloride extended-release) tablets

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known May 27, 2016

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)(1)

b) 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.

Three clinical studies were completed by the applicant, one study for bioavailability (Study 1288.8) and two studies for bioequivalence (Studies 1288.9 and 1288.11) were completed. Per the note above, BA and BE studies do not qualify. The applicant acknowledges only BA and BE studies were completed for this application, they refer to NDA 201280 and have right of reference to NDA 021748 for safety and efficacy.

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

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

N/A

d) 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#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA#	NDA 201280	Tradjenta (linagliptin) tablets
NDA#	NDA 021748	Glumetza (metformin extended-release) tablets
NDA#	NDA 201281	Jentadueto (linagliptin and metformin) tablets

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☐ NO ☐

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

(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:

(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:

(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:

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 ☐

Investigation #2 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:

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 ☐

Investigation #2 YES ☐ NO ☐

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

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"):

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 # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(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:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(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:

==========

Name of person completing form: Richard Whitehead, M.S.
Title: DMEP RPM
Date: May 27, 2016

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: DMEP Director

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

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

/s/

RICHARD E WHITEHEAD
05/27/2016

JEAN-MARC P GUETTIER
05/27/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208026	
Proprietary Name: Jentadueto XR Established/Proper Name: linagliptin and metformin hydrochloride extended-release Dosage Form: 2.5 mg/1000 mg and 5 mg/1000 mg tablets	Applicant: Boehringer Ingelheim Pharmaceutical, Inc
RPM: Richard Whitehead	Division: Division of Metabolism and Endocrinology Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)	**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☐ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: ***Note: 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 May 27, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? 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 ____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] 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.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 4-New Combination
(confirm chemical classification at time of approval)

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

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

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
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

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)*	AP; May 27, 2016
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)*	☒ Included see action letter dated: May 27, 2016
• Original applicant-proposed labeling	☐ Included
❖ 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)*	☒ Included see action letter dated: May 27, 2016
• Original applicant-proposed labeling	☐ Included
❖ 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	☒ Included see action letter dated: May 27, 2016
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	9-16-15 9-15-15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: PLR Format 9-15-15 DMEPA: 4-29-16; 3-15-16 DMPP/PLT: 5-05-16 OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: DPMH PLLR 5-02-16
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	9-15-15 ☒ Not a (b)(2)
❖ 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

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• 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 4-13-16 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	5-27-16; 5-3-16; 3-24-16; 10-02-15; 9-18-15; 9-14-15; 7-31-15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	1-06-15
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
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)*	☐ None 5-27-16
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 5-27-16
• Clinical review(s) *(indicate date for each review)*	5-18-16; 9-24-15
• 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)*	See clinical review (page 11) dated: 5-18-16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(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
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	4-27-16; 10-2-15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	3-31-16; 3-15-16(2); 2-19-16; 12-09-15

For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5-04-16; 9-11-15
❖ 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
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	4-18-16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ 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)*	4-18-16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: n/a

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

From: Whitehead, Richard
To: "renee.zindell@boehringer-ingelheim.com"
Subject: RE: NDA208026 Jentadueto XR: labeling
Date: Friday, May 27, 2016 12:03:00 PM
Attachments: Jentadueto XR_US PI-final clean-27 May 2016.pdf
image001.png

Renee,

We note your agreement to the NDA208026 Jentadueto XR labeling dated May 27, 2016. I have attached a PDF version of the clean copy you sent at 11:48AM. I will contact if we need anything else.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: renee.zindell@boehringer-ingelheim.com [mailto:renee.zindell@boehringer-ingelheim.com]
Sent: Friday, May 27, 2016 11:48 AM
To: Whitehead, Richard
Subject: RE: NDA208026 Jentadueto XR: labeling

Dear Richard,

BI agrees with all the revisions which were proposed by FDA. The final agreed upon label (clean version) is attached. I will follow up with a formal submission which contains the identical version to the application.

With kind regards,
Renee

Boehringer Ingelheim

Renee Zindell, M.S., RAC
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, May 27, 2016 10:26 AM
To: Zindell,Renee (MED RA) BIP-US-R

Subject: NDA208026 Jentadueto XR: labeling

Renee,

The reviewers are asking for additional edits on pages 3, 5, 6, and 10. These additional deletions were required (b) (4) for which this product is contraindicated.

The above attached label, if changes are accepted by you, can be considered final. We will need this back as soon as possible with a similar email that you provided below.

With regard to their question about parity, we intend to harmonize changes across labels.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: renee.zindell@boehringer-ingelheim.com [mailto:renee.zindell@boehringer-ingelheim.com]
Sent: Friday, May 27, 2016 9:30 AM
To: Whitehead, Richard
Subject: NDA208026 Jentadueto XR: labeling

Dear Richard,

BI agrees with all the revisions which were proposed by FDA. The final agreed upon label (clean version) is attached. I will follow up with a formal submission which contains the identical version to the application.

We noted in preparation of this label that (b) (4), which is why we thought it reasonable to include it initially. However, we understand the FDA's position and wondered if we can expect to see alignment with respect to this study across the class?

With kind regards,
Renee

Renee Zindell, M.S., RAC
Regulatory Affairs

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Zindell,Renee (MED RA) BIP-US-R
Sent: Friday, May 27, 2016 7:29 AM
To: 'Whitehead, Richard'
Subject: RE: NDA208026 Jentadueto XR: labeling

Thank you. Will get back to you regarding the (b) (4), which is the only outstanding item at this point.

Renee Zindell, M.S., RAC
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, May 27, 2016 7:23 AM
To: Zindell,Renee (MED RA) BIP-US-R
Subject: RE: NDA208026 Jentadueto XR: labeling

Renee,

Your proposed changes to section 12..3 Pharmacokinetics (on page 9 of the PI) are acceptable.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: renee.zindell@boehringer-ingelheim.com [mailto:renee.zindell@boehringer-ingelheim.com]
Sent: Thursday, May 26, 2016 7:57 PM
To: Whitehead, Richard
Subject: RE: NDA208026 Jentadueto XR: labeling

Dear Richard,

Do you think you will provide feedback for the first comment before tomorrow morning?

With kind regards,
Renee

Boehringer Ingelheim

Renee Zindell, M.S., RAC
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, May 26, 2016 7:08 PM
To: Zindell,Renee (MED RA) BIP-US-R
Subject: NDA208026 Jentadueto XR: labeling

Renee,

We are deleting the [redacted] (b) (4) from the proposed Jentadueto XR label. (b) (4) [redacted]. Note that in the future [redacted] (b) (4) should be removed from the Jentadueto label as well. Please delete your second comment as it is no longer relevant. I have followed up regarding your first proposed change and will provide a response ASAP.

Send a clean version with all edits accepted via email and submit a copy to your application. Note that we need to receive your final agreed labeling by 10AM Friday May 27, 2016. We will be unable to take an action without agreed labeling.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: renee.zindell@boehringer-ingelheim.com [mailto:renee.zindell@boehringer-ingelheim.com]
Sent: Thursday, May 26, 2016 5:05 PM
To: Whitehead, Richard
Subject: RE: NDA208026 Jentadueto XR: labeling

Dear Richard,

Please find attached the proposed label for Jentadueto XR. We have included the statement

noted below to address FDA's question related to the [redacted] (b) (4)

Please let me know if we should plan to make a formal submission to provide this document as well.

With kind regards,
Renee

Renee Zindell, M.S., RAC
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, May 26, 2016 2:16 PM
To: Zindell,Renee (MED RA) BIP-US-R
Subject: RE: NDA208026 Jentadueto XR: labeling

Thank you

From: renee.zindell@boehringer-ingelheim.com [mailto:renee.zindell@boehringer-ingelheim.com]
Sent: Thursday, May 26, 2016 2:00 PM
To: Whitehead, Richard
Subject: RE: NDA208026 Jentadueto XR: labeling

Dear Richard,

Thank you for your quick response. We have discussed the FDA revisions and are routing them to management for approval before sending the word document back. I will have it to you later today.

With kind regards,
Renee

Renee Zindell, M.S., RAC
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]

Sent: Thursday, May 26, 2016 1:21 PM
To: Zindell,Renee (MED RA) BIP-US-R
Subject: RE: NDA208026 Jentadueto XR: labeling

Renee,

Your proposal to include the statement [redacted] (b) (4)
Is acceptable.
You should also address the question related to the [redacted] (b) (4).

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: renee.zindell@boehringer-ingelheim.com [mailto:renee.zindell@boehringer-ingelheim.com]
Sent: Thursday, May 26, 2016 1:00 PM
To: Whitehead, Richard
Subject: RE: NDA208026 Jentadueto XR: labeling

Dear Richard,

BI is requesting clarification for the FDA comment:

clarify why this study is included in this label. [redacted] (b) (4)

We can hereby notify you that [redacted] (b) (4)

BI is proposing to add a statement to address FDA's comment:

[redacted] (b) (4)

Given the limited timeframe remaining to discuss the labeling, could you please clarify if this would be acceptable to include?

With kind regards,
Rene

Boehringer Ingelheim

Renee Zindell, M.S., RAC
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5419 :: F:203 778 7880
renee.zindell@boehringer-ingelheim.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, May 26, 2016 9:56 AM
To: Zindell,Renee (MED RA) BIP-US-R
Subject: NDA208026 Jentadueto XR: labeling

Renee,

There are two comments that need to be addressed for your NDA208026 Jentadueto XR labeling. Please provide responses to those questions via email as soon as possible. We also need final agreed labeling therefore we need all edits agreed to and a clean copy sent to me via email followed by submission to your application. After I receive responses to the questions and a clean version I will confirm with the review team that the labeling is acceptable and let you know that the labeling can be submitted as final agreed labeling to NDA208026.

Please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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

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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/

RICHARD E WHITEHEAD
05/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND (b) (4)

**MEETING REQUEST-
WRITTEN RESPONSES**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Renee Zindell, M.S., RAC
Manager, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Zindell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for linagliptin and metformin extended-release, fixed dose combination tablets.

We also refer to your submission dated November 7, 2014, containing a pre-NDA meeting request. The purpose of the requested meeting was to review clinical, nonclinical, and quality items prior to submission of your New Drug Application (NDA).

Further reference is made to our Meeting Granted letter dated November 25, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 4, 2014, background package.

If you have any questions, call Richard Whitehead, M.S., Senior Regulatory Project Manager at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA
Application Number:	(b) (4)
Product Name:	linagliptin and metformin extended-release tablets
Indication:	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes where treatment with both linagliptin and metformin hydrochloride extended-release is appropriate
Sponsor/Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Boehringer Ingelheim (BI) is the New Drug Application (NDA) holder for both Tradjenta (linagliptin) tablets and Jentadueto (linagliptin/metformin hydrochloride) tablets and has obtained a right of reference and full access to utilize the information included within the NDA for Glumetza (metformin hydrochloride extended-release) tablets. All of these products have been approved by FDA.

BI is developing linagliptin and metformin hydrochloride extended-release (ER) fixed dose combination (FDC) tablets intended as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes where treatment with both linagliptin and metformin hydrochloride extended-release is appropriate. Linagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Previous FDA regulatory interactions include a pre-IND (Type B) and subsequent Type C meeting regarding the development of this ER FDC, with written responses obtained on both occasions, which are dated October 11, 2011, and June 26, 2013, respectively.

During the aforementioned interactions agreement was reached on a "Phase I only" program in support of registration which compares co-administration of single entity tablets linagliptin and metformin hydrochloride extended-release to the 'to be marketed' ER FDC for each tablet strength under fed and fasted conditions. The results allow bridging of the existing safety and efficacy data from studies with following to the proposed ER FDC:

- Tradjenta (linagliptin) tablets
- Jentadueto (linagliptin and metformin hydrochloride) tablets
- Glumetza (metformin hydrochloride extended-release) tablets

BI has completed the Phase I pivotal studies which have demonstrated bioequivalence within the range of 80.00-125.00% for all tablet strengths tested. BI is planning to submit these clinical studies, in conjunction with cross referencing to the full data from the approved NDA's bulleted above and drug product information, as NDA 208026 under the 505(b)1 pathway in third quarter of 2015.

The purpose of the meeting is to ensure that BI has fully addressed all development plans and standards prior to submission of their NDA. BI will has provided quality, nonclinical, and clinical safety and efficacy data as part of this meeting.

2.0 QUESTIONS AND RESPONSES

2.1. Chemistry, Manufacturing, and Controls

Question 1: *a) Does the Division concur with the proposed approach for Module 3 for the linagliptin and metformin HCl extended release (ER) coated tablets NDA? b) Does the Division concur with the proposal for the QOS documentation of the NDA?*

FDA Response to Question 1a: Yes, we agree with the proposed format and content of Module 3 of the future NDA.

FDA Response to Question 1b: Yes, we agree with the proposed content of Module 2 (QOS) of the future NDA.

Question 2: *Does FDA agree with BI's proposal to include the metformin salt form in the drug product name?*

FDA Response to Question 2: Yes, we agree with your proposed established name "metformin hydrochloride" because the strength is based on the salt form.

2.2. Nonclinical

Question 3: *Does the Division have any comments related to the proposed cross referencing plan as outlined in the Module 1.4.4 document found in Appendix 4?*

FDA Response to Question 3: Your plan to cross reference nonclinical studies from your other applications is acceptable.

Question 4: *a) Does the Division concur with the proposal for Module 4 of the NDA? b) Does the Division concur with the proposal for the Module 2 nonclinical summary documentation of the NDA?*

FDA Response to Question 4a: Your plan to use cross references of nonclinical data from other applications in Module 4 is acceptable.

FDA Response to Question 4b: We agree that Nonclinical Written and Tabulated Summaries are not required for Module 2.6 based on the absence of new nonclinical studies. We request you submit a Nonclinical Overview in Module 2.4 to clarify how the cross referenced nonclinical data was used to support this new drug product and to facilitate an efficient review by the Division.

2.3. Clinical

Question 5: *Does the Division have any comments about the general organization, proposed content, and cross-referencing plans pertaining to Module 5?*

FDA Response to Question 5: The proposed plan is reasonable.

Question 6: *Does the Division concur with or have additional comments related to the proposed case report tabulation datasets in CDISC, SDTM, CRFs and safety narratives planned for this linagliptin and metformin extended-release FDC tablet NDA?*

FDA Response to Question 6: In addition to subjects who discontinued from Phase 1 studies due to an adverse event, we request that you submit case report forms and narrative for all subjects who experienced serious adverse events (SAE) even if the SAE did not lead to discontinuation from the study.

Question 7: *a) Does the Division concur with this proposal of not including Module 2 clinical summary documents? b) Does the Division concur with the proposal concerning ISE/ISS documents for this NDA?*

FDA Response to Question 7a: We agree that Clinical Summaries are not required for Module 2.7. However, we request that you submit a Clinical Overview (Module 2.5) and discuss how the cross referenced clinical data was used to support this new drug product, present an overview of clinical data (e.g., Phase 1 studies), and any other relevant clinical summary in order to facilitate an efficient review by the Division.

FDA Response to Question 7b: We concur with your proposal to not submit ISE/ISS documents as only Phase 1 studies have been conducted for this NDA.

Question 8: *Does the Division concur with the proposal concerning the 4-month safety update?*

FDA Response to Question 8: No we do not agree. You should submit a 4-month safety update as required by regulation. Your 4-month safety update should include any relevant post-marketing data and any relevant information from medical literature.

Question 9: *Does the Division have any comments that can be shared at this time for the above referenced PSP?*

FDA Response to Question 9: We do not have any comments to share at this time. Full comments will be provided within 90 days of your iPSP submission date.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 25, 2014, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is

the actual physical site(s) where documents are maintained and would be available for inspection

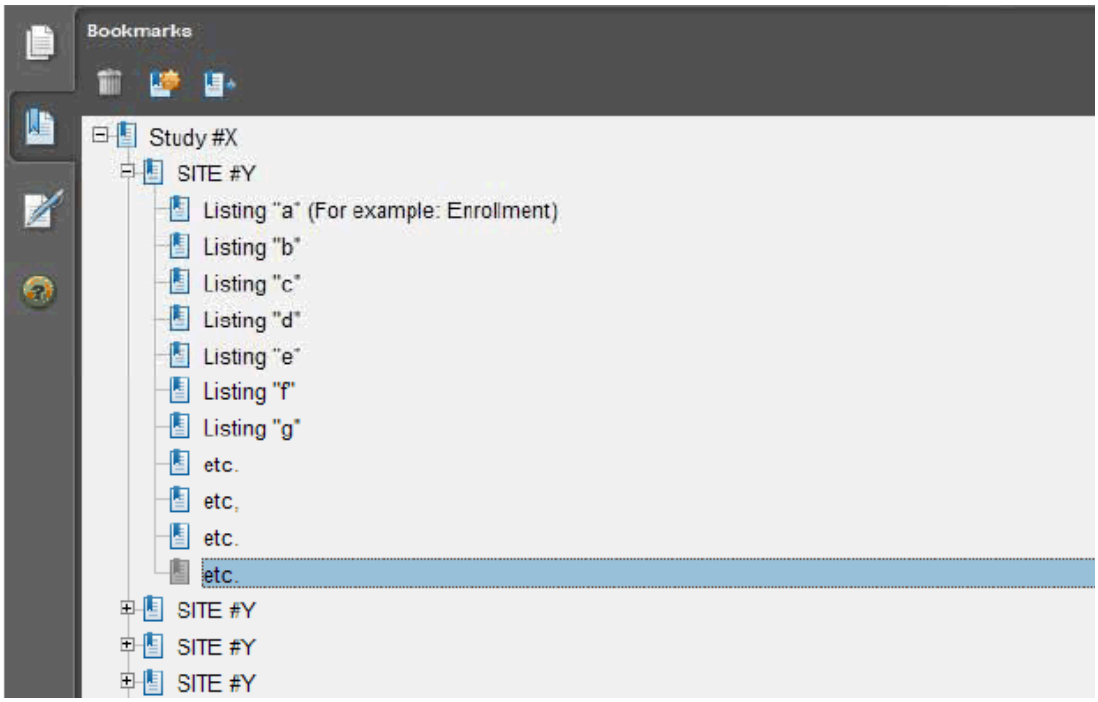
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

JEAN-MARC P GUETTIER
01/06/2015

From:	Whitehead, Richard
To:	M. S. RAC Renee Zindell (renee.zindell@boehringer-ingelheim.com)
Subject:	NDA208026 Jentadueto XR labeling
Date:	Friday, April 29, 2016 3:48:00 PM
Attachments:	NDA208026-201281 proposed Labeling 4-29-16.docx

Renee,

I am returning your NDA208026 Jentadueto XR proposed labeling with FDA comments. Please review the comments and accept all comments and edits that you agree with and remove comment boxes associated with those edits. For comments that you do not agree with add a comment box with your requested changes and justification. Please include a statement, "BI comment", as the comments boxes can get confusing. As discussed please remove all reference to (b) (4) in this Jentadueto XR label.

Please return your proposed labeling with accepted edits or new comments by **Open-of-Business May 9th**. Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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

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/s/

RICHARD E WHITEHEAD
05/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208026

GENERAL ADVICE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Renee Zindell, M.S., RAC
Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Zindell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets.

We also refer to your July 27, 2015, and March 11, 2016, submission, containing your proposed carton and container labeling.

We recommend the following be implemented prior to approval of this NDA:

1. Container Labels
    a. We recommend increasing the font size of the strength to improve prominence and readability, and to mitigate the potential for wrong strength errors
    b. Revise the statement (b) (4) to as follows, to ensure consistency between Jentadueto XR and Jentadueto: "Dispense the accompanying medication guide to each patient"

2. Carton Labeling
    a. See recommendations 1.b

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, 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/

JENNIFER R PIPPINS
03/24/2016
Signed on behalf of Dr. Guettier

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208026

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Renee Zindell, M.S., RAC
Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Zindell:

Please refer to your New Drug Application (NDA) dated and received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Jentadueto XR (linagliptin and metformin HCl extended-release) tablets.

We also refer to your amendments dated July 27, 28, and August 6, 2015.

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 **May 27, 2016**.

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, mid-cycle, 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 **April 27, 2016.**

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

Your proposed dissolution acceptance criteria for the metformin extended release component at the (b) (4) and are therefore, not acceptable. Since no established In Vivo In Vitro Correlation of metformin hydrochloride (HCl) is submitted in this NDA application for the final drug product (linagliptin/metformin HCl extended-release

fixed dose combination tablets, 2.5mg/1000mg and 5mg/1000mg), the final acceptance criteria of metformin HCl need [redacted] (b) (4) to [mean±10% (Quantity)] for the first and second sampling time points. The final determination of dissolution acceptance criteria will be made after a thorough review based on the totality of the dissolution profile data submitted to NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

The hyperlinks to the safety narratives for subjects with serious adverse events and adverse events leading to discontinuation from Phase 1 studies provided in Table 5.4: 3 of Clinical Overview are not correctly linked to narratives. Please resubmit the table with correct hyperlinks.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents;
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances; and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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.

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your requests, we will notify you if these requests are denied.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, 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/

JEAN-MARC P GUETTIER
10/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208026

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Renee Zindell, M.S., RAC
Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Zindell:

Please refer to your New Drug Application (NDA) dated and received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for linagliptin and metformin HCl extended-release fixed dose combination tablets.

We are reviewing the clinical pharmacology 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.

1. Submit the subject level electronic data for Study 1288.10 including at minimum dosing (i.e., period, sequence, treatment/formulation, meal condition), demographic and pharmacokinetic data, preferably as SAS transport (*.xpt) files.

2. Provide final bioequivalence analysis ready data sets (i.e. Subject ID, Period, Sequence, Treatment/Formulation, Meal Condition, PK parameters such as AUC and Cmax in a single dataset) for all studies (i.e., 1288.8, 1288.9, 1288.10 and 1288.11) as SAS transport (*.xpt) files.

If you have any questions, please contact Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, 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/

RICHARD E WHITEHEAD
09/18/2015
Signed on behalf of Jean-Marc Guettier, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208026

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Renee Zindell, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Zindell:

Please refer to your New Drug Application (NDA) dated and received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linagliptin and Metformin HCl Extended-Release Tablets, 5 mg/1000 mg and 2.5 mg/1000 mg.

We also refer to your correspondence dated and received July 27, 2015, requesting review of your proposed proprietary name, Jentadueto XR.

We have completed our review of the proposed proprietary name, Jentadueto XR and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 27, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Richard Whitehead, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

TODD D BRIDGES
09/16/2015

From: Whitehead, Richard
To: M. S. RAC Renee Zindell (renee.zindell@boehringer-ingelheim.com)
Subject: NDA208026 linagliptin and metformin XR: Information Request
Date: Friday, August 07, 2015 3:49:00 PM

Renee,

In reference to you July 26, 2015 new NDA submission of linagliptin and metformin XR (NDA208026), please see the following request for information:

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, we noted that you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information on metformin and linagliptin use in pregnant and lactating women by ***October 7, 2015****:*

- *a review and summary of all available published literature regarding metformin and linagliptin use in pregnant and lactating women*
- *a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.*

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidance.

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301 796 4945; (f) 301 796 9712; richard whitehead@fda hhs gov

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/s/

RICHARD E WHITEHEAD
09/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208026

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Renee Zindell, M.S., RAC
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Zindell:

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

Name of Drug Product: linagliptin and metformin hydrochloride extended-release fixed dose combination 2.5mg/1000mg and 5mg/1000mg tablets

Date of Application: July 27, 2015

Date of Receipt: July 27, 2015

Our Reference Number: NDA 208026

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 Friday, September 25, 2015in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RICHARD E WHITEHEAD
07/31/2015