

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201280Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

***For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use***

NDA NUMBER

201280

NAME OF APPLICANT/NDA HOLDER

Boehringer Ingelheim Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ONDERO

ACTIVE INGREDIENT(S)

Linagliptin

STRENGTH(S)

5 mg

DOSAGE FORM

Tablet (oral)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 7,407,955	b. Issue Date of Patent August 5, 2008	c. Expiration Date of Patent August 12, 2023
d. Name of Patent Owner Boehringer Ingelheim Pharma GmbH & Co., K.G.	Address (of Patent Owner) Binger Strasse 173	
	City/State Ingelheim	
	ZIP Code Germany	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Boehringer Ingelheim Pharmaceuticals, Inc.	Address (of agent or representative named in 1.e.) 900 Ridgebury Road	
	City/State Ridgefield/CT	
	ZIP Code 06877-0368	FAX Number (if available) 203-798-4408
	Telephone Number 203-798-9988	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes

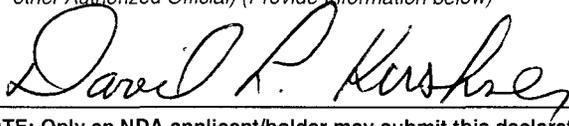
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



05/24/2010

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

David L. Kershner

Address

900 Ridgebury Road

City/State

Ridgefield/CT

ZIP Code

06877-0368

Telephone Number

203-798-9988

FAX Number (if available)

203-798-5469

E-Mail Address (if available)

david.kershner@boehringer-ingelheim.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 201280

SUPPL # N/A

HFD # 510

Trade Name Tradjenta Tablets

Generic Name linagliptin

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known

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)

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.

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:

d) Did the applicant request exclusivity?

YES NO

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

5 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?

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#

NDA#

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:

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: Raymond Chiang
Title: Consumer Safety Officer
Date: 3.22.11

Name of Office/Division Director signing form: Mary Parks, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

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

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

/s/

RAYMOND S CHIANG
04/29/2011

ILAN IRONY
04/29/2011
I concur.

DEBARMENT CERTIFICATION

Certification Requirement Section 306(k)(1) 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: Christopher D Corsico

Name of Applicant: Christopher Corsico, M.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 4 June 2010

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

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

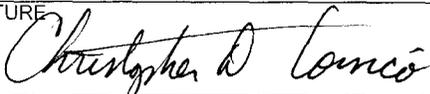
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attached list of sites for study numbers:	
	1218.5, 1218.6, 1218.15, 1218.16, 1218.17, 1218.18	
	1218.20, 1218.23, 1218.35, 1218.50	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Christopher Corsico, MD, MPH	TITLE U.S. Regional Medical Director
FIRM/ORGANIZATION Boehringer Ingelheim Pharmaceuticals, Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 4 June 2010

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

MEMORANDUM OF TELECON

MEETING DATE: April 19, 2011
TIME: 9:00 am EST
APPLICATION: NDA 201280
DRUG NAME: Tradjenta (linagliptin)

MEETING RECORDER: Raymond Chiang, M.S.

FDA ATTENDEES: (Title and Office/Division)

Mary Parks, M.D.	Division Director, DMEP
Curt Rosebraugh, M.D., M.P.H.	Office Director, ODEII
Ilan Irony, M.D.	Diabetes Clinical Team Leader, DMEP
Somya Verma, M.D.	Clinical Reviewer, DMEP
Raymond Chiang, M.S.	Regulatory Project Manager, DMEP
Amy Egan, M.D., M.P.H.	Deputy Director of Safety
Xiao Ding, Ph.D.	Biometrics Reviewer
Matt Soukup, Ph.D.	Biometrics Team Leader
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II (DBII)

EXTERNAL CONSTITUENT ATTENDEES:

Klaus Dugi, M.D.	Corporate Senior Vice President Medicine
Sabine Luik, M.D.	Corporate Senior Vice President QM, Regulatory Affairs, Pharmacovigilance, Epidemiology
Christopher Corsico, M.D.	US Regional Medical Director
Hans-Juergen Woerle, M.D.	Vice President Therapeutic Area Metabolism
John Smith, M.D.	Senior Vice President Clinical Development and Medical Affairs
Joanne Palmisano, M.D.	Vice President, Drug Regulatory Affairs-US
Sanjay Patel, M.D.	Team Member Medicine Linagliptin
Mathias Senger, Ph.D.	International Project Management
Thomas Rauch, M.D.	International Project Management
Dietmar Neubacher, Ph.D.	Project Statistician Linagliptin
Paul Bispham, Ph.D.	Team Member RA Linagliptin, Global Regulatory Affairs
Maureen Oakes, PharmD	Sr Associate Director DRA Product Group-US
Beth Weinberg, RPh	Global Regulatory Affairs-US (Eli Lilly)
Heidi Reidies, M.S.	Executive Director DRA Product Group-US

SUBJECT: Discussion of CAROLINA trial and PMR for a cardiovascular safety trial for linagliptin (NDA 201280)

TELECONFERENCE:

BI questioned why FDA was now requesting a placebo-controlled cardiovascular outcomes trial given FDA's agreement in August 2010 for BI to conduct an active-controlled cardiovascular outcomes trial using glimepiride as comparator to satisfy the PMR.

FDA stated that the cardiovascular safety of sulfonylureas is unknown, and showing non-inferiority, or even superiority, to a drug (glimepiride) that may have adverse cardiovascular risks would not establish that linagliptin does not cause cardiovascular events. Dr. Rosebraugh reviewed for BI the rationale behind the requirement for all new anti-diabetic therapies to establish that there is not a cardiovascular risk that is intrinsic to the agent itself and noted that all trials currently underway for anti-diabetic drugs as PMR commitments are placebo-controlled. Dr. Rosebraugh added that the CAROLINA trial would be of interest to the FDA and to clinicians as the cardiovascular safety of sulfonylurea agents has long been question. However, CAROLINA, would not answer the question that is the basis for the requirement of CV assessment which is does linagliptin itself carry a risk of cardiovascular harm, not whether it is comparable to another agent, particularly one with an unknown cardiovascular safety profile.

BI argued that standard of care is frequently sulfonylureas. BI would not be able to incorporate a third placebo arm because the CAROLINA trial is already recruiting well, and because all patients are already on metformin therapy.

FDA stated that BI will need to perform as a PMR a cardiovascular trial that will allow for a primary comparison of linagliptin cardiovascular safety to placebo in some form, either as an additional arm to CAROLINA or in an additional stand alone placebo-controlled trial.

BI asked whether future meta-analysis of other ongoing and future trials, trying to combine those trials with placebo arms, would satisfy the CV-safety PMR, if it rules out the 1.3 risk threshold. Dr. Rosebraugh stated that he did not think this approach would answer the primary question outlined above.

FDA stated that if the sponsor decided that incorporating a placebo arm into CAROLINA was not feasible at this time, that only a stand alone trial against placebo would satisfy the CV-safety PMR. FDA stated that they were still interested in the CAROLINA results, but again, even if linagliptin would show a non-inferior or superior CV-risk profile over glimepiride, there would still be doubts as to the cardiovascular safety of linagliptin compared to placebo.

BI understood and committed to conducting a trial against placebo to satisfy the CV-safety PMR. BI provided the following tentative dates for the CV-safety PMR:

Final Protocol Submission:	June 2012
Study Completion:	October 2018
Final Report Submission	May 2019

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

/s/

RAYMOND S CHIANG
04/21/2011

MEMORANDUM OF TELECON

MEETING DATE: April 15, 2011
TIME: 4:00 pm EST
APPLICATION: NDA 201280
DRUG NAME: Tradjenta (linagliptin)

MEETING RECORDER: Raymond Chiang, M.S.

FDA ATTENDEES: (Title and Office/Division)

Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Raymond Chiang, M.S.	Regulatory Project Manager, DMEP

EXTERNAL CONSTITUENT ATTENDEES:

Maureen Oakes, Pharm.D.	Associate Director, Regulatory Affairs, US
Heidi Reidies, M.Sc.	Executive Director, Regulatory Affairs, US

SUBJECT: Discussion of CAROLINA trial and CV-safety PMR for linagliptin (NDA 201280)

TELECONFERENCE:

The Division applauded BI for conducting CAROLINA, but was concerned that without a placebo arm or a placebo-controlled trial, and especially because of the safety concerns with glimepiride, it will not be possible to evaluate the cardiovascular (CV) safety of linagliptin versus other marketed drugs. The Division also stated that this position was strongly supported, by Office of New Drug Evaluation II (C. Rosebraugh), and Office of New Drugs (J. Jenkins).

The Division stated that even if study 20 demonstrates that linagliptin has a lower CV risk compared to glimepiride, this was not reassuring because glimepiride may have a higher CV risk compared to other therapies. In other words, even if linagliptin demonstrates less CV risk compared to glimepiride, it may still have higher CV risk compared to other marketed drugs.

Options offered by the Division would be to add a third arm to CAROLINA, placebo on top of standard of care, or a non-inferiority study comparing linagliptin versus placebo (with standard of care). The primary objective of either study to meet the FDA PMR requirements would need to be a non-inferiority comparison of linagliptin versus placebo. The comparison of linagliptin versus glimepiride would be a secondary objective. The Division added that this was in line with what other companies were doing.

With either approach (CAROLINA w/ placebo arm or new placebo-controlled non-inferiority study), BI will need to provide FDA with key PMR dates shortly (final protocol, study completion, study report) in order to meet PDUFA dates.

The Division suggested that if BI demonstrates that the CV risk profile for linagliptin is no worse than other marketed drugs and superior to glimepiride, this could be a possible claim.

The Division noted that the meeting on Tuesday could be used to iron out any questions BI might have on the design of the proposed placebo-controlled study(s); alternatively, BI could cancel the meeting. BI noted that we would get back to the Division by close of business on Monday on whether the meeting would be canceled.

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

/s/

RAYMOND S CHIANG
04/26/2011



NDA 201280

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

Attention: Maureen Oakes, Pharm.D.
Senior Associate Director
Drug Regulatory Affairs

Dear Dr. Oakes:

Please refer to your New Drug Application (NDA) dated July 2, 2010, received July 2, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linagliptin Tablets, 5 mg.

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

The proposed proprietary name, Tradjenta, 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 February 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 Raymond Chiang at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
04/08/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: FW: info request 4.6.11
Date: Wednesday, April 06, 2011 9:16:06 AM

Hi Maureen,
See information request below. Please respond ASAP.
As always, please confirm receipt of this email.
thanks,
ray

Please provide narrative/specifics on the AEs of anaphylactic reaction, angioedema, and severe cutaneous adverse reactions of mouth and skin ulceration below. This is a table from their CSR for 1218.18.

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/s/

RAYMOND S CHIANG
04/06/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Information request--- linagliptin
Date: Monday, April 04, 2011 1:39:34 PM

Hi Maureen,
Please see information request below. As usual, please respond ASAP and confirm receipt of this email.
thanks,
ray

Please provide narratives on the skin exfoliation cases that occurred in the linagliptin program

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/s/

RAYMOND S CHIANG
04/06/2011

Ripper, Leah W

From: Greeley, George
Sent: Tuesday, April 05, 2011 11:07 AM
To: Chiang, Raymond
Cc: Addy, Rosemary; Mathis, Lisa; Parks, Mary H; Ripper, Leah W; Suggs, Courtney
Subject: NDA 201-280 Linagliptin

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Raymond,

The email serves as confirmation of the review for Linagliptin conducted by the PeRC PREA Subcommittee on March 16, 2011.

The Division presented a partial waiver for patients birth through nine years of age and a deferral for patients ten to ^{(b) (4)} years of age for the indication of treatment of patients with type 2 diabetes mellitus.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product. The pediatric record is attached for Linagliptin.



1_Pediatric_Record
pdf (62 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.

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingenheim.com"](mailto:maureen.oakes@boehringer-ingenheim.com);
Subject: RE: F/U Information request--- linagliptin
Date: Monday, April 04, 2011 8:58:04 AM

Hello Maureen,

Thank you for your response to our earlier information request.
We also have the following follow-up requests (in black font) below.
Please respond ASAP. As usual, please confirm receipt of email.

thanks,
ray

1. When will BI be sending the final clinical trial report for Study 1218.20 to the FDA? Will the trial report include raw datasets?

2. In light of the event rates for CV death, nonfatal MI, and nonfatal stroke from Study 1218.20, please provide a sample size calculation for CAROLINA based on a primary endpoint of time to first occurrence of CV death, nonfatal MI and nonfatal stroke (i.e., traditional MACE).

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/s/

RAYMOND S CHIANG
04/04/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Information request--- linagliptin
Date: Friday, April 01, 2011 10:00:56 AM

Hello Maureen,

Please see information request (in black font) below. Please respond ASAP.

Please confirm receipt of this email.

thanks,

ray

Based on the 52-week interim analysis of Study 1218.20, the incidence of the primary composite endpoint of CV death, NFMI, NFstroke, and hospitalization for UA was 0.4% in linagliptin and 2.6% in glimepiride. Please provide FDA with an update of the incidence of these events in both treatment groups since the interim analysis.

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/s/

RAYMOND S CHIANG
04/01/2011

MEMORANDUM OF TELECON

MEETING DATE: March 25, 2011
TIME: 10:00 am EST
APPLICATION: NDA 201280
DRUG NAME: Tradjenta (linagliptin)

MEETING RECORDER: Raymond Chiang, M.S.

FDA ATTENDEES: (Title and Office/Division)

Ilan Irony, M.D.	Diabetes Clinical Team Leader, DMEP
Somya Verma, M.D.	Clinical Reviewer, DMEP
Raymond Chiang, M.S.	Regulatory Project Manager, DMEP
John Bishai, Ph.D.	Safety Regulatory Project Manager
Amy Egan, M.D., M.P.H.	Deputy Director of Safety
Enid Galliers	Chief Project Manager
Xiao Ding, Ph.D.	Biometrics Reviewer
Matt Soukup, Ph.D.	Biometrics Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

H.J. Woerle, M.D.	Therapeutic Area Head, Metabolism
P. Bispham, PhD.	Global Regulatory Affairs
J. Palmisano	VP, US Regulatory Affairs
T. Rauch, M.D.	Project Leader, Linagliptin
M. Senger, M.D.	International Project Management
S. Patel, M.D.	Team Member Medicine, Clinical Research
D. Collette,	Associate Director, US Regulatory Affairs
B. Weinberg, RPh	Director, Global Regulatory Affairs, Lilly
M. Oakes, Pharm.D.	Sr. Associate Director, US Regulatory Affairs

SUBJECT: Discussion of CAROLINA trail and CV-safety PMR for linagliptin (NDA 201280)

TELECONFERENCE:

Pediatrics (PMR)

FDA requested timelines for both pediatric studies (does-finding study, safety and efficacy study). Timelines include dates for submission of final protocol, trial completion and final report submission. Note that protocol is considered final only after FDA and BI have agreed on study design.

For the pediatric safety and efficacy study, FDA requested that patients on metformin background therapy be evaluated, either by adding two additional arms (cohorts of subjects randomized to placebo or to linagliptin on a metformin background therapy) to the currently proposed study or by conducting a separate study randomizing subjects on metformin background therapy to either linagliptin or to placebo.. BI understood. FDA would like the information regarding dates and our decision regarding the above bullet by COB on Tuesday, 29 March.

Renal

FDA would like timelines for the two renal studies (1218.43 and 1218.64). Timelines include date for submission of final report.

CV (PMR)

FDA requested that a randomized, double-blind, placebo-controlled trial be conducted rather than current 1218.74 study vs. glimepiride. FDA also requested that the following secondary objectives be included: immunological reactions, hypersensitivity reactions, neoplasms, severe hypoglycemia, pancreatitis and renal safety.

BI expressed that the 1218.74 study was agreed upon by the Agency prior to initiation. FDA stated that they had always had reservations with glimepiride as an active-control comparator.

FDA indicated that the reason for requesting a placebo-controlled trial was because of concern regarding the uncertainty of the cardiovascular risk associated with glimepiride. FDA indicated that if there is no comparison to placebo, and only a comparison to glimepiride, that there would still be lingering doubts as to the cardiovascular safety of linagliptin compared to placebo, and in relation to other drugs in the class.

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/s/

RAYMOND S CHIANG
04/20/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com";](mailto:maureen.oakes@boehringer-ingelheim.com)
Subject: RE: Comments regarding linagliptin carton and container labels submitted March 17, 2011
Date: Thursday, March 24, 2011 4:46:34 PM

Hi Maureen,

Please see comments regarding linagliptin carton and container labels submitted March 17, 2011.

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

We find [REDACTED] (b) (4)

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

As per our conversation, please officially submit the revised carton and container labels addressing our issues by next Thursday, March 31, 2011.

thanks,

ray

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/s/

RAYMOND S CHIANG
03/24/2011

MEMORANDUM

Between: Ilan Irony, M.D. (HFD-510)
Diabetes Team Leader
Somya Dunn, M.D. (HFD-510)
Diabetes reviewer
And: J. Todd Sahlroot, Ph.D. (HFD-715)
Deputy Director and Team Leader

Subject: NDA 201280 Tardjenta ¹ (linagliptin) 5mg for treatment of patients with type 2 diabetes Submitted by Boehringer Ingelheim Pharmaceuticals Inc on July 2, 2010

Wei Liu, Ph.D., submitted a statistical review of linagliptin to DARRTS on March 11, 2011. His review addressed the efficacy of linagliptin in type 2 diabetes based on the results of seven Phase 3 clinical trials (Studies 15,16,17,18, 20, 35 and 50). The primary efficacy endpoint in each trial was change from baseline in HbA1c. Based on his efficacy conclusions, with which I agree, there is substantial evidence of efficacy. I recommend approval for this application.

¹ The trade name Tardjenta is currently under review by DMEPA

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/s/

JON T SAHLROOT
03/14/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE:linagliptin label
Date: Thursday, March 10, 2011 1:47:06 PM
Attachments: [linagliptin PI 3.10.11 emailed to sposnor.doc](#)

Hi Maureen,

See attached linagliptin label reflecting DMEP's comments and proposed changes.

Please accept all FDA edits that you agree with. So, the document 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.

Please leave our original comment bubbles in the label. This will make sure tracked changes show which FDA review made the edits (will be useful for showing which edits come from our various disciplines vs. which edits were BI's)---- otherwise, all edits only show up as "author."

You only need to add a comment bubble responding to our original 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 of our original comment bubbles necessarily need to have an accompanying response comment bubble from you.

Please see your revised label to us by COB, March 17, 2011.
Please do not hesitate to call or email if you have any questions.
As usual, please confirm receipt of email.

thanks!
ray

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

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/s/

RAYMOND S CHIANG
03/10/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Question regarding linagliptin
Date: Wednesday, March 09, 2011 9:45:25 AM

Hello Maureen,

Please see below (in black font) information request from the medical officer. Please confirm receipt.

Please reply by COB today.

thanks!

ray

At the End of Phase 2 (EOP2) meeting on December 11, 2007, we made the following comment:

FDA: (For the active control trial, study 20), the Sponsor should not perform an unblinded interim analysis on efficacy variables but keep the blind for the efficacy outcome variables until the end of the study hypothesis testing at Week 104.

You did submit interim data for this study. The study report assures that investigators and patients remained blinded. Who in your company had access to this data? How is the integrity of this study being maintained in terms of sponsor access?

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/s/

RAYMOND S CHIANG
03/09/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingenheim.com"](mailto:maureen.oakes@boehringer-ingenheim.com);
Subject: RE: Question regarding linagliptin
Date: Tuesday, March 08, 2011 8:51:08 AM

Hi Maureen,

Please see below question (in black font) regarding linagliptin from the medical officer and stats review. Please respond ASAP.

thanks!

ray

In your study report for 1218.20, the FAS is defined as:*The primary analysis was performed on the full analysis set (FAS). The FAS consisted of all randomised patients who were treated with at least one dose of study medication, had a baseline HbA1c measurement, and had at least one on-treatment HbA1c measurement.*

And FAS completers are defined as:

The FAS-completers comprised all patients in the FAS who completed at least 323 days i.e., 46 weeks of treatment and had a HbA1c measurement at Visit 10.

However, in your recent cover letter, 2/25, you state that the FAS is patients that had at least 46 weeks of treatment.

Please clarify this discrepancy.

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/s/

RAYMOND S CHIANG
03/08/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com)
Subject: RE: Linagliptin (NDA 201280)
Date: Monday, March 07, 2011 9:34:29 AM

Hi Maureen,

Please see comments below (in black font) regarding the linagliptin carton and container labels submitted on February 1, 2011. Please email and submit this within 10 days.

thanks!
ray

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

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

B. Carton Labeling (Rx sample)

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

C. Blister Foil Label

1. Remove [REDACTED] (b) (4). If feasible, consider grouping the [REDACTED] (b) (4) together, and place the three empty cavities together. This configuration would minimize the risk of confusion [REDACTED] (b) (4).
2. Remove "[REDACTED] (b) (4)" from the blister foil labels. Linagliptin is a Once Daily medication used primarily by patients at home [REDACTED] (b) (4).

Also, as per our phone conversation, because the proprietary trade name is still pending, please produce carton and container and blister foil labels with only the established name on them. You can email and submit these at a later date. Please confirm receipt of this email.

thanks!
ray

From: Tossa, Margarita
Sent: Friday, March 04, 2011 8:57 AM
To: 'maureen.oakes@boehringer-ingelheim.com'; Chiang, Raymond
Subject: RE: Linagliptin (NDA 201280)
Importance: High

Dear Maureen,

Comments from the DMEPA re: carton and container labeling were provided to the Division on February 15, 2011, and I will refer to Raymond Chiang re: when comments were or will be conveyed to you.

Proposed TN is under review.

Thank you,

Margarita

From: maureen.oakes@boehringer-ingelheim.com [mailto:maureen.oakes@boehringer-ingelheim.com]
Sent: Friday, March 04, 2011 6:22 AM
To: Tossa, Margarita
Cc: Chiang, Raymond
Subject: Linagliptin (NDA 201280)

Dear Margarita:

I am contacting your to inquire about the review of "Tradjenta", the proposed proprietary name for linagliptin the review of our carton and container labels for the product. Do you have any comments for us at this point? If not, do you know when we might expect to receive comments. Any information which you are able

to share would be most appreciated. Thank you.

Kind regards,

Maureen

*Maureen Oakes, Pharm.D.
Sr. Associate Director
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
Telephone: 203.798.5723
Email: maureen.oakes@boehringer-ingelheim.com*

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/s/

RAYMOND S CHIANG
03/07/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingenelheim.com"](mailto:maureen.oakes@boehringer-ingenelheim.com);
Subject: RE: Linagliptin Information request 2.11.11
Date: Friday, February 11, 2011 3:33:52 PM

Hi Maureen,

See below information request from the FDA medical officer. Please respond within 3 business days. Also, I am planning our next internal labeling meeting. Can you confirm that the most recently submitted label was February 4, 2011 and that you do not plan to submit any more labels until labeling negotiations begin.

thanks!

ray

1. You state in your Summary of Clinical Safety (SCS), that in SAF-2 2565 patients were treated with linagliptin 5 mg. You state that 1183 patients received placebo. Before the datasets for study 37 were submitted, we pooled all the other study datasets for SAF-2 (except study 37). We made the following table based on treatment arm and demographics:

GLIMEPIRIDE	65
LINAGLIPTIN 0.5 MG	58
LINAGLIPTIN 2.5 MG	59
LINAGLIPTIN 5 MG	55
LINAGLIPTIN 1 MG	74
LINAGLIPTIN 10 MG	254
LINAGLIPTIN 2.5 MG	35
LINAGLIPTIN 5 MG	2474
METFORMIN	63
PBO - LINAGLIPTIN 5 MG - LINAGLIPTIN 10 MG	41
PBO - LINAGLIPTIN 5 MG - LINAGLIPTIN 5 MG	39
PBO + GLI	76
PLACEBO	989
VOGLIBOSE - VOGLIBOSE - LINAGLIPTIN 10 MG	81
VOGLIBOSE - VOGLIBOSE - LINAGLIPTIN 5 MG	81

If we add the number of patients from study 37 to those taking linagliptin 5mg presented in this table, the total N is the same as what you report in your SCS. However, we cannot find the correct combination of arm to get 1183 for placebo patients. Please describe how the arms other than linagliptin arms were coded (i.e. were patients getting metformin also getting placebo?). Perhaps you can explain how to recover the 1183 (minus any patients from study 37) placebo treated patients from this table.

2. Please calculate the treatment-years for placebo patients in SAF-2.

Please send this information within 3 business days.

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/s/

RAYMOND S CHIANG
02/11/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Linagliptin information request 2.10.11
Date: Thursday, February 10, 2011 11:23:08 AM

Hi Maureen,

See information request (in black font) below from the FDA pharm tox reviewer. Please respond ASAP.

There is a problem with one of the genetic toxicity study reports submitted for an impurity. Please contact the sponsor concerning the following study report:

*Document No. U08-2200-01 (Study 08B126) (b) (4)
(b) (4) (Impurity of BI 1356):
Mutagenicity study using the S. typhimurium/
mammalian-microsome assay (Ames test)*

The sponsor submitted "Amendment #1" of the study report which is a brief update (7 page document) that didn't change the

conclusions of the study but it has no data in it. However, I cannot find any submission of the complete study report. The amendment is in the original NDA submission (7/2/10), eCTD section 4.2.3.7.6. I suspect this was an oversight and they meant to also submit the full study report with the amendment.

Please submit the complete study report by email ASAP or to direct me to the submission within the NDA. If they've submitted it to IND 70,963 I may be able to find it there but I haven't found it yet.

*thanks!
ray*

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/s/

RAYMOND S CHIANG
02/10/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Linagliptin information request 2.9.11
Date: Wednesday, February 09, 2011 3:29:53 PM

Hi Maureen,

See information request (in black font) below from the statistical reviewer. Please respond ASAP.
Please confirm receipt of email.

thanks!

ray

We have the following request related to the datasets 'pcecst.xpt' and 'pcecst2.xpt' submitted to FDA on December 22, 2010 (sequence 0017)

1. Please update both datasets by adding the following three variables for each subject included in the datasets:

- Baseline Age (continuous variable in the unit of year)
- Baseline BMI in (continuous variable in the unit of kg/m²)
- Baseline eGFR (MDRD) (continuous variable in the unit of mL/min)

Please submit the updated datasets ASAP.

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/s/

RAYMOND S CHIANG
02/09/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: Linagliptin information request 2.4.11
Date: Friday, February 04, 2011 4:14:19 PM

Hi Maureen,

See the information request from the FDA medical officer:

A. In your Summary of Clinical Safety on page 40 you state that 3430 patients with T2DM were exposed to 5 mg linagliptin for 6 months or longer. SAF-2 has 2566 of these patients and SAF-4 has 778 of these patients (total 3344). Are the missing 86 patients in the uncontrolled extension study 1218.40?

B. Please construct the following tables in pdf format. They should be concise and should draw upon data already presented in your Summary of Clinical Safety (SCS) or Integrated Summary of Safety (ISS). You may also need the study report for 1218.20. The data are available, so please send these tables within 7 business days. Thank you.

1. Using data presented in Section 5 of your SCS, please construct two pdf tables (one for SAF-2 and SAF-4). Each table should list the subgroup and the overall adverse event (AE) incidence by linagliptin and placebo/comparator. There should be no details on type of AE, SOC, etc. Only the overall incidence of AE by subgroup.

2. Construct a pdf table similar to the one in the four month safety update, table 2.1.2: 1, page 60 that includes ALL deaths, not just phase III and uncontrolled extension. It should have the same categories (exposure, etc).

3. Construct a pdf table that shows concise laboratory abnormality incidences for SAF-2 as seen in Table 12.4: 1, page 119 for clinical study report for study 1218.20. Table 6.1.2.1 in your ISS displays several labs that are not abnormal and is formatted and organized differently.

4. Using the tables in your ISS, section 2.6.5.3, beginning with Table 6.5.3.1, please construct a table for all labs listed here for SAF-3. This table should give only the lab, the change from baseline to week 24 for linagliptin and for the placebo. It should have the mean +/- SD, and underneath, the median with (minimum, maximum) as seen below:

Laboratory

Linagliptin

Placebo

N=650

N=169

Potassium (mEq/L)	-0.018±0.030	0.024±0.032
	0.000 (-0.076, 0.040)	0.000 (-0.039, 0.088)

5. For SAF-3, table 6.1.3.1 in the ISS, please construct a table that displays the possible clinically significant laboratory incidence by parameter and by linagliptin or placebo. It should look similar to below with linagliptin treated group as one column and placebo as the other:

Parameter	N=247	N=252
Hemoglobin < 8 g/dL	0 (0)	1/247 (0.4)
Hematocrit <0.75X pre-Rx	1/242 (0.4)	2/247 (0.4)

BEST AVAILABLE COPY

6. Please construct tables for SAF-4 (study 1218.20) similar to those requested in #4 & 5.

Also, can you tell the status regarding the information request sent to you on 1.20.11 at 4:29 PM EST. See below in red font.

thanks!
ray

From: Chiang, Raymond
Sent: Thursday, January 20, 2011 4:29 PM
To: 'maureen.oakes@boehringer-ingelheim.com'
Subject: RE: Linagliptin information request 1.20.11

Hi Maureen,

See another information request (in black font) from the medical officer:

1. Updated to the Four Month Safety Update cutoff, a full adverse event (AE) analysis of SAF-2 (cumulative as your other 4MSUs analyses are). Your current MSU-2, as you indicated, is divided into two different groups. Please send the SAME single grouping presented in the original NDA. When you send this, please make sure there is a table, by System Organ Class (SOC) for serious adverse events. Please include two pdf formatted tables for this, one with the frequent preferred terms for the SAE and one without (with just the SOC). Otherwise, you can follow the format you generally use in your Summary of Clinical Safety and your 4MSU for AE presentation.

2. Full combined datasets (xpt) for SAF grouping, SAF-2.

3. Please also submit xpt database for study 37.

Please prioritize the first request and send all of this information within 3 business days. You should already have this information on hand, as you used SAF-2 as a main part of your SCS and ISS. If this is not the case and this cannot be sent soon, please explain.

Please confirm receipt of this email.

thanks!

ray

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/s/

RAYMOND S CHIANG
02/04/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Linagliptin information request 1.20.11
Date: Thursday, January 20, 2011 4:29:00 PM

Hi Maureen,

See another information request (in black font) from the medical officer:

1. Updated to the Four Month Safety Update cutoff, a full adverse event (AE) analysis of SAF-2 (cumulative as your other 4MSUs analyses are). Your current MSU-2, as you indicated, is divided into two different groups. Please send the SAME single grouping presented in the original NDA. When you send this, please make sure there is a table, by System Organ Class (SOC) for serious adverse events. Please include two pdf formatted tables for this, one with the frequent preferred terms for the SAE and one without (with just the SOC). Otherwise, you can follow the format you generally use in your Summary of Clinical Safety and your 4MSU for AE presentation.

2. Full combined datasets (xpt) for SAF grouping, SAF-2.

3. Please also submit xpt database for study 37.

Please prioritize the first request and send all of this information within 3 business days. You should already have this information on hand, as you used SAF-2 as a main part of your SCS and ISS. If this is not the case and this cannot be sent soon, please explain.

Please confirm receipt of this email.

thanks!

ray

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/s/

RAYMOND S CHIANG
01/25/2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Proprietary name review

Meeting Date and Time: January 19, 2011, 11:00 AM to 12:00 PM EST
Meeting Location: Teleconference, WO 4322, Bldg 22

Application Number: 201280
Product Name: Linagliptin
Indication: Glycemic control in adults with type 2 diabetes mellitus
Sponsor/Applicant Name: Boehringer Ingelheim

Meeting Chair: Zach Oleszczuk
Meeting Recorder: Nina Ton

FDA ATTENDEES

Lena Maslov, Safety Evaluator, DMEPA
Manizheh Siahpoushan, Safety Evaluator, DMEPA
Zach Oleszczuk, Team Leader, DMEPA
Nina Ton, Safety Regulatory Project Manager, OSE
Darrell Jenkins, Team Leader, Project Management, OSE

SPONSOR ATTENDEES

Mathias Senger, MD, Project Leader, International Project Management
Juergen Roemhilds, Head of Corporate Department Intellectual Property Rights & Unfair Competition, Corporate Vice President
Heidi Reidies, MS, Executive Director, Drug Regulatory Affairs, US
Maureen Oakes, Pharm.D., Sr. Associate Director, Drug Regulatory Affairs, US
Joanne Palmisano, MD, Vice President, Drug Regulatory Affairs

1. BACKGROUND

Boehringer Ingelheim (BI) submitted a request for the review of the proprietary name, Trajenta on November 19, 2010. The Division of Medication Error Prevention and Analysis (DMEPA) has evaluated the proposed proprietary name Trajenta and concluded that the name is unacceptable. (b) (4)

The purpose of the teleconference was to communicate DMEPA's objection to the proposed proprietary name and to discuss options for a path forward.



DMEPA advised BI the options for moving forward. The first option is to wait for the completion of the review which is due February 17, 2011. The second is to withdraw the proposed proprietary name Trajenta and to submit the secondary proposed proprietary name, (b) (4). The last option is to withdraw the proposed proprietary name Trajenta and submit a different alternate name.

BI plans to have an internal team discussion and will notify the FDA of their decision. During the teleconference, the applicant expressed a concern that after the proprietary name for a single ingredient Linagliptin product is accepted and marketed, (b) (4)

DMEPA responded that although similar naming convention has been used, the risk of medication errors with this particular naming strategy would have to be evaluated in addition to the entire safety assessment in order to determine name approvability.

BI requested comments on the carton and container labels. DMEPA responded that the review is in progress. OND will send comments to the applicant when the review is finalized.

3. ACTION ITEMS

Boehringer Ingelheim will respond by the end of next week.

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/s/

PHUONG N TON
02/07/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com"](mailto:maureen.oakes@boehringer-ingelheim.com);
Subject: RE: Linagliptin information request 1.19.11
Date: Wednesday, January 19, 2011 1:55:17 PM

Hi Maureen,

Please see [another information request from the medical officer](#):

Please specify where in the NDA submission you have a combined DATASET for your SAF groupings? We are specifically looking for the AE datasets for SAF-2 and SAF-4--with ALL adverse events, that specifies all parameters such as treatment arm, study, serious AE, etc.

If you could address this information request soon, that would be great.

thanks!
ray

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/s/

RAYMOND S CHIANG
01/25/2011

From: Chiang, Raymond
Sent: Friday, January 14, 2011 11:45 AM
To: 'maureen.oakes@boehringer-ingelheim.com'
Subject: RE: Linagliptin information request 1.14.11

Hi Maureen,

See information requests (in black font) from the FDA medical officer:

Please answer this question regarding Serious Adverse Events (SAEs) within two days (you do not need to provide anything). In the 4 Month Safety Update (4MSU), for MSU-2A, it appears that SAEs reported in Table 5.2.2.1.6.1 occurred later than those submitted in the original NDA (reported in the Summary of Clinical Safety). Rates are similar between those reported for SAF-2 and MSU-2A. The number of patients reported for treatments changed according to who finished the trials. This is expected for an update. Regarding study 1218.20 (MSU-4) the number of patients reported for the treatment groups remains the same, the post treatment numbers went up. The SAEs are different in number, but if **combined** with those reported in the NDA, the rate of SAEs is much higher. We are aware of the difference in MedDRA versions, but this does not explain the increase in SAE rate. Does Table 5.2.4.6.1.1 display SAEs that occurred since those reported in the NDA? Or are these ALL the SAEs that occurred in this trial at the point of the 4MSU cutoff? This is not clear. If you included ALL SAEs in the trial, this is not consistent with what is reported in other parts of the 4MSU.

Pertaining to the Cardiovascular Meta-analysis: In your Cardiovascular Meta-analysis, Table 6 breaks down cardiovascular risk factor (baseline CV characteristics) by treatment group for all the analyzed studies. Can you please provide a similar table for each individual study that was included in the meta-analysis? Please prioritize Study 1218.20, and send this within a week, or sooner if possible. The rest of the tables may follow within another week. Please include the same parameters as Table 6.

Pertaining to the whole NDA: Were there any deaths in patients that were screened for the any of the studies but were not randomized? If so, where is this information located in the application?

Please confirm receipt of this email.

thanks!

ray

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/s/

RAYMOND S CHIANG
01/14/2011

From: [Chiang, Raymond](#)
To: ["maureen.oakes@boehringer-ingelheim.com";](mailto:maureen.oakes@boehringer-ingelheim.com)
Subject: RE: Statistics request for CV metanalysis-- NDA 201280 linagliptin
Date: Tuesday, December 14, 2010 2:03:07 PM

Hi Maureen,

Please respond to this information request (in black font below) within 10 days of receipt of this email. Please confirm receipt of this email.

thanks!
ray

Ondera NDA 201280

At this time, the statistical review of your meta-analysis is not able to reproduce the results provided in your meta-analysis report dated May 28, 2010 ('1218-p1-metaanalysis--01-10--report.pdf' in section 5.3.3. u10-1736- Cardiovascular meta-analyses). Please provide the following information to facilitate the review of your application.

1. Please provide the specific analysis dataset(s) used in your cardiovascular meta-analysis.
2. Please clarify the differences among the following terminologies used for meta-analysis results based on the CMH test:
 - § 'CMH test (treatment arm cc)' and 'Stratified CMH test' in Table 8 on page 29,
 - § 'Stratified CMH (treatment arm continuity correction)' in Table 9 on page 31, and
 - § 'CMH test (treatment arm cc)' in Table 12 on page 35.
3. For all the results shown in Figure 2, Figure 4, and Figure 6, as all as in Table 8, Table 9, and Table 12, please provide detailed information pertaining to the statistical methods used in the calculation of all point estimates and confidence intervals. For example, what variables were included in the Cox regression model and in the Poisson regression model? What method is used to compute the stratified exact odds ratio? What is the value of continuity correction and when will the continuity correction be used?
4. For all the statistical methods covered in Item 3, please provide the name of the statistical software used, along with the version number, used in the derivation of results. If SAS was

used, also please provide the executable SAS codes.

5. For each of the pooled analysis results shown in Figure 2 and Figure 4, please also provide the exact list of studies that contributed to that result.

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/s/

RAYMOND S CHIANG
01/25/2011

From: Chiang, Raymond
Sent: Friday, December 10, 2010 11:54 AM
To: 'maureen.oakes@boehringer-ingenelheim.com'
Subject: RE: Information request for NDA 201280

Hi Maureen,

See information request below. Please respond no later than Thursday, December 16th.

thanks!
ray

**Information Request
NDA 201280 Linagliptin
December 10, 2010**

Study 1218.20

Please provide a table of **FAS** patients for the following:

1. For treatment weeks, 12-52, please provide a dataset, or similar table, showing each patient and what dose of glimepiride that patient was on. If the dose was changed during that time, please clarify that with a study week designation, not an actual date. The number of rows should roughly correspond to the number of patients in this treatment arm (approx 750).
2. Please also send a table showing what number of patients was on what glimepiride dose during this treatment time. Please include standard deviations and total mean doses. You can organize this by time group (i.e. weeks 12-28, weeks 28-40, weeks 40-52), but be sure to include a mean total for the entire treatment time as well (12-52).
3. Also, for **the same dose and time groupings**, present in a separate table if needed, which patients at which doses had rescue medication. I would also like to see the study discontinuations and reason for discontinuations presented in a similar manner (by dose and treatment time).
4. Please clarify why dose titrations were set to 4 mg of glimepiride only. We understand that is this usual maintenance dose; however, you have conducted a noninferiority study. A total of 8 mg is the maximum treatment for this medication. Why was this not used as the active comparison?

Study 1218.15

5. Please explain your rationale for using pioglitazone for **initial therapy** versus as an ongoing therapy (with linagliptin or placebo add on) as the other pivotal studies (17 and 18) were designed?

Please provide the requested information by Thursday December 16th. Please prioritize the first two requests.

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/s/

RAYMOND S CHIANG
12/10/2010



NDA 201280

INFORMATION REQUEST

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

Dear Ms. Oaks:

Please refer to your new drug application (NDA) originally submitted on July 2, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Linagliptin Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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 Substance



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If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

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

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/s/

ALI H AL HAKIM
12/08/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 17, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: Information request--- treatment identifier code

From: Chiang, Raymond
Sent: Wednesday, November 17, 2010 11:28 AM
To: 'maureen.oakes@boehringer-ingelheim.com'
Subject: RE: Linagliptin (201280) Information Request--- treatment identifier code

Hi Maureen,

The statistical reviewer looked at the ADBASCO.xpt dataset of study 1218.20 (1218-0020ia) and the variable TRTP contained "BLIND" only. Please submit your version of ADBASCO.xpt.

thanks!
ray

From: maureen.oakes@boehringer-ingelheim.com [mailto:maureen.oakes@boehringer-ingelheim.com]
Sent: Monday, November 15, 2010 12:32 PM
To: Chiang, Raymond
Subject: RE: Linagliptin (201280) Information Request

Dear Raymond:

Attached is a brief response to the question below. Would you kindly let me know if further information is needed.

The information on the patient treatment assignment can be found in ADBASCO.xpt, variable TRTP. Treatment code 500 represents 'LINAGLIPTIN 5 MG', treatment code 920 represents 'GLIMEPIRIDE'.

Thank you.

Maureen

Maureen Oakes, Pharm.D.
Sr. Associate Director
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
Telephone: 203.798.5723
Email: maureen.oakes@boehringer-ingelheim.com

Reference ID: 2865086

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

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]

Sent: Sunday, November 14, 2010 10:10 PM

To: Oakes,Dr.,Maureen DRA BIP-US-R

Subject: RE: Linagliptin (201280) Information Request

Hi Maureen,

Please see information request from our statistical reviewer. As always, please response as soon as possible.

Please send the treatment identifier code from the 52-week efficacy dataset of study 1218.20, otherwise, your results as listed in their proposed label Section 14.2 Table 4 will not be evaluable. If they are in the database, please advise where they are. If they are not there, please send them.

thanks!

ray

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/s/

RAYMOND S CHIANG
11/17/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 17, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: Information request 11.17.10 regarding efficacy analysis without rescue medication

From: Chiang, Raymond
Sent: Wednesday, November 17, 2010 11:14 AM
To: 'maureen.oakes@boehringer-ingenelheim.com'
Subject: RE: Linagliptin (201280) Information Request--- efficacy analysis not include rescue

Hi Maureen,

I was just following up on the information request below. If you could provide this info soon, that would be great.
thanks!
ray

From: Chiang, Raymond
Sent: Monday, November 15, 2010 1:40 PM
To: 'maureen.oakes@boehringer-ingenelheim.com'
Subject: RE: Linagliptin (201280) Information Request

Hi Maureen,

Please see below (in black font) an information request from our clinical reviewer. As always, please respond as soon as possible.
thanks!
ray

What efficacy analysis does NOT include patients that had rescue (in the pivotal trials)? Where in the submission is this analysis?

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/s/

RAYMOND S CHIANG
11/17/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 3, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: Information request NDA 201280

From: Chiang, Raymond
Sent: Wednesday, November 03, 2010 10:33 AM
To: 'maureen.oakes@boehringer-ingelheim.com'
Subject: RE: Linagliptin (201280) Information Request

Please see information request (in black font) regarding NDA 201280:

Please provide the Berkeley Madonna code for the final pharmacokinetic model of linagliptin which was used to assess the clinical relevance of statistically significant covariates. You have referred to it in section 8.4.1.4.4 of population pharmacokinetic analysis report for linagliptin. Please submit the code within 10 days.

Please confirm receipt of this email.
thanks!
ray

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/s/

RAYMOND S CHIANG
11/03/2010

DATE: 22-Oct-2010

TO: NDA 201-280 (5 mg linagliptin tablets) Inspection Team

FROM: Olen Stephens, Ph.D. 301-796-3901; olen.stephens@fda.hhs.gov

THROUGH: Christine Moore, Ph.D.

SUBJECT: Considerations for Inspection during the pre-approval or post-approval inspections at Boehringer Ingelheim Roxane Inc. (1510690)

Introduction:

NDA 201-280 is submitted by Boehringer Ingelheim for 5 mg linagliptin tablets, which is a relatively high solubility, low permeability drug indicated for Type 2 diabetes mellitus. This memo provides a brief overview of the drug product manufacturing process including elements of Quality by Design (QbD) that may be considered on inspection.

The 5-mg linagliptin tablets intended for commercial distribution are round, biconvex, film-coated, light red-colored, immediate-release tablets. (b) (4)

The film coating is non-functional. (b) (4)

The applicant has not presented a formal risk analysis, but prior knowledge was used to designate content uniformity, assay, and dissolution as critical quality attributes (CQA). The applicant claims that (b) (4) are critical unit operations. My preliminary review suggests (b) (4) can affect dissolution performance of the final drug product.

(b) (4) is well defined and appropriate in-process controls (Attachment 3) are in place such that there are no major quality concerns identified in the application at this time, if the firm operates as described in the application. Furthermore, the dissolution

method is discriminatory and likely to detect changes in the manufacturing process that affect product quality.

As part of our commitment to share QbD information across our Offices, the CMC review team submits the following risk items of the manufacturing process for consideration while on inspection:



The CMC reviewer is willing to share his knowledge with the investigator prior to and during the inspection. If you have any questions, please email or call the CMC reviewer Olen Stephens, Ph.D. – 301-796-3901; olen.stephens@fda.hhs.gov

The following information is provided as an aid to your inspection:

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/s/

OLEN M STEPHENS
10/22/2010

ALI H AL HAKIM
10/22/2010



NDA 201280

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

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

Attention: Maureen Oakes, PharmD
Senior Associate Director
Drug Regulatory Affairs

Dear Dr. Oakes:

Please refer to your New Drug Application (NDA) dated July 2, 2010, received July 2, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linagliptin Tablets, 5 mg.

We also refer to your July 9, 2010, correspondence, received July 9, 2010, requesting review of your proposed proprietary name, Ondero. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

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 Raymond Chiang at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Denise Toyer, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
10/07/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 22, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: RE: information request #1 included in the attached linagliptin filing letter

From: Chiang, Raymond
Sent: Wednesday, September 22, 2010 11:52 AM
To: 'maureen.oakes@boehringer-ingelheim.com'
Subject: Re: information request #1 included in the attached linagliptin filing letter
Importance: High

Hi Maureen,

Sorry it took me so long to reply to you.
Please see the medical reviewer's response (in black italics font):

We can continue our review of the NDA with the files we have already in the edr (eCTD).

thanks,
ray

From: maureen.oakes@boehringer-ingelheim.com [mailto:maureen.oakes@boehringer-ingelheim.com]
Sent: Tuesday, September 14, 2010 9:24 AM
To: Chiang, Raymond
Subject: RE: Filing Letter for NDA 201280 (Linagliptin)

Dear Ray:

Thank you again for providing comments on the linagliptin NDA. Would you kindly provide additional guidance pertaining to the first comment in the "Clinical" section below:

"Both the ISE and ISS in the linagliptin NDA are in tabular form only. Please send a revised version that contains textual explanations for the tables presented."

At the time of the pre-NDA meeting, BI proposed via Question 7 of pre-NDA meeting package that the Summary of Clinical Safety (Module 2.7.4) be used to fulfill the requirements of the text portion of the ISS. We indicated that the supportive listings, tables, and figures would be placed in the ISS in Module 5.3.5.3. The same approach was detailed for the SCE/ISE. We understood that this approach for the ISS and ISE was acceptable and that the descriptions would be appropriately placed in the SCS and SCE, respectively.

Does the Division accept this strategy to have the tables, listings and figures in the ISE/ISS and the description in the SCE/SCS? Your input would be greatly appreciated.

Many thanks,

Maureen

*Maureen Oakes, Pharm.D.
Sr. Associate Director
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
Telephone: 203.798.5723
Email: maureen.oakes@boehringer-ingelheim.com*

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

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Monday, September 13, 2010 5:03 PM
To: Oakes,Dr.,Maureen DRA BIP-US-R
Subject: RE: Filing Letter for NDA 201280 (Linagliptin)
Importance: High

See attached. Please confirm receipt.
thanks!
ray

From: maureen.oakes@boehringer-ingelheim.com [mailto:maureen.oakes@boehringer-ingelheim.com]
Sent: Monday, September 13, 2010 4:45 PM
To: Chiang, Raymond
Subject: Re: Filing Letter for NDA 201280 (Linagliptin)

Dear Ray:

Thank you for your e-mail. Yes, we would appreciate it if you could send a copy of the letter electronically.

Kind regards,

Maureen

Sent from my BlackBerry Wireless Handheld

From: Chiang, Raymond <Raymond.Chiang@fda.hhs.gov>
To: Oakes,Dr.,Maureen DRA BIP-US-R
Sent: Mon Sep 13 16:38:16 2010
Subject: RE: Filing Letter for NDA 201280 (Linagliptin)
Maureen,

The filing letter for NDA 201280 (linagliptin) has been mailed to you. Please advise whether you also want this letter by email or not.

thanks!
ray

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/s/

RAYMOND S CHIANG
09/22/2010



NDA 201280

FILING COMMUNICATION

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 Dr. Oakes:

Please refer to your new drug application (NDA) dated July 2, 2010, received July 2, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Linagliptin tablet, 5 mg.

We also refer to your submission dated July 7 and 9, August 2, 3, and 25, and September 2, 2010.

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 2, 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 March 23, 2011.

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

CLINICAL:

1. Both the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the linagliptin NDA are in tabular form only. Please send a revised version that contains textual explanations for the tables presented.

2. Your NDA is based on data derived largely from international sites. Submit your rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.
3. As some of your studies are ongoing, clarify your plan to submit updated analyses of cardiovascular safety based on accrued cardiovascular events for contributing to the overall linagliptin cardiovascular meta-analysis. This plan should be submitted prior to the four month safety update.

LABELING:

General Comments:

4. Use command language throughout the label.
5. Please add line numbering to the Package Insert Word Document.

Highlights Section:

6. Please do not bullet/indent the indication statement or the “Important limitations of use” heading.
7. Please add white space between indication statement and Important Limitations of Use.
8. Please use bullets to itemize statements under the “Important limitations of use” heading. Please also capitalize the first letter of each statement (i.e. Should not be used in patients with type 1 diabetes.....).
9. In the CONTRAINDICATIONS, please do not list theoretical possibilities (i.e. hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reactions.

Full Prescribing Information (FPI):

10. In the DOSAGE FORMS AND STRENGTHS, please clarify whether “D5” is printed on one side and whether the Boehringer Ingelheim logo is printed on the reverse side. See approved Onglyza package insert for appropriate language.
11. In the CONTRAINDICATIONS, please do not list theoretical possibilities (i.e. hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reactions. If no contraindications are known, this section must state “None”.
12. In the DRUG INTERACTIONS, please insert the cross references (i.e. see Clinical Pharmacology (12.3)) at the end of each paragraph.

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.

Please respond to the above requests, including revised labeling, within 21 days of the date of this letter unless specified otherwise. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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 partial waiver of pediatric studies for patients <10 years of age because T2DM “is not commonly seen in this age group.” All waiver requests must include supporting information and documentation to support the waiver request. We note that you did not submit the supporting information and documentation. Please submit the required supporting information and documentation for your partial waiver request. Once we have received the additional data, we will review your request, and we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for 10 years of age (b) (4) “to ensure sufficient safety and efficacy data were first collected in adult patients.” However, you did not provide data to support this request. All deferral requests must include supporting information and documentation to support the deferral request. We note that you did not submit the supporting information and documentation. Please submit the required supporting information and documentation for your partial deferral request. Once we have received the additional data, we will review your request, and we will notify you if the partial deferral request is denied.

Within 30 days of the date of this letter, please submit your pediatric plan outlining the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that you plan to conduct to meet the PREA requirements. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) sufficient to demonstrate dose, safety, and efficacy. The pediatric plan must contain a timeline for the completion of pediatric studies, i.e. the dates 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. (See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>).

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity, consult the Division of Metabolism and Endocrinology Drug Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Raymond Chiang, Consumer Safety Officer, at (301) 796-1940.

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

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

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/s/

MARY H PARKS
09/09/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 8, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: Information requested regarding DSI sponsor inspections NDA 201280 (linagliptin)

From: maureen.oakes@boehringer-ingelheim.com [mailto:maureen.oakes@boehringer-ingelheim.com]
Sent: Wednesday, September 08, 2010 8:57 AM
To: Chiang, Raymond
Subject: RE: Information requested regarding NDA201280 (linagliptin)

Dear Ray:

This e-mail is to confirm that I received your request below. I will contact Dr. Leibenhaut if I need further clarification. Kind regards, Maureen

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

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Wednesday, September 08, 2010 8:55 AM
To: Oakes,Dr.,Maureen DRA BIP-US-R
Subject: RE: Information requested regarding NDA201280 (linagliptin)
Importance: High

Maureen,

Please see information requested below (in black font) regarding NDA201280 (linagliptin).

Please include the following information in a tabular format for the following clinical trials:

- a. Protocol 1218.15 entitled "A randomized, double-blind, placebo controlled, parallel group 24 week study to assess the efficacy and safety of BI 1356 (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug naive or previously treated type 2 diabetic patients with insufficient glycemic control"
- b. Protocol 1218.16 entitled "A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks, in drug naive or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycemic control"
- c. Protocol 1218.17 entitled "A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite metformin therapy"
- d. Protocol 1218.18 entitled "A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg) administered orally

once daily over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite a therapy of metformin in combination with a sulphonylurea”

1. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.) for each clinical trial noted above. These documents are sometimes referred to as the “clinical trial master file.”
2. Name, address and contact information of all Contract Research Organizations (CROs) used in the conduct of each clinical trial noted above..
3. Please state whether the primary endpoint data for Hemoglobin A1C is located at the clinical sites. (i.e. whether clinical sites were not blinded to the endpoint HbA1C and were provided with the results during or after the trial).
4. Please state whether the cardiology and neurology Clinical Endpoint Committees (CEC) were the same for all four clinical trials. Please provide the location of the adjudication data base archive.

Please contact Dr. Susan Leibenhaut for any questions concerning the above requests.

Please provide this information by email and as a official amendment to the NDA ASAP. Also, please confirm receipt of this email.

thanks!

ray

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

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/s/

RAYMOND S CHIANG
09/08/2010

From: Chiang, Raymond
Sent: Tuesday, August 24, 2010 12:08 PM
To: 'maureen.oakes@boehringer-ingenelheim.com'
Subject: RE: From FDA: Information request from statistical reviewer associated with NDA 201280 (Linagliptin)
Importance: High

Maureen,

Please see attached information request from our statistical reviewer. Please provide your response by email and officially as an amendment to the NDA by September 3, 2010. Please confirm receipt of this email.

Also, can you give me the status of my information request, emailed to you on August 23, 2010 at 11:27 AM EST, regarding the clinical sites. If you have any questions, please do not hesitate to call.

thanks!
ray

Ondera NDA-201280

We have the following requests for clarification pertaining to the Analysis CE Dataset ('adpc.xpt') and the Statistical Analysis CE Dataset ('adpcstat.xpt').

1. According to the define file, variable **TRTP** is populated with the planned treatment sequence code the subject is assigned/randomized to. In Study 1218-0020ia, variable **TRTP** is supposed to have code value 'AA005' or 'AG001'. However, in the Statistical CE Dataset ('adpcstat.xpt'), every subject had **TRTP**='BLIND'. Please explain the discrepancy between the dataset and the define file.
2. For all the phase 3 studies including Study 1219-0020ia, please check the Analysis CE Dataset ('adpc.xpt') and the Statistical Analysis CE Dataset ('adpcstat.xpt') to make sure that all variables and decodes are consistent with the define files.

Please clarify the discrepancies noted and should revised data sets be needed, the Agency requests these be submitted in a timely fashion.

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/s/

RAYMOND S CHIANG
01/25/2011



NDA 201280

NDA ACKNOWLEDGMENT

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 Dr. Oakes:

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 tablet, 5 mg

Date of Application: July 2, 2010

Date of Receipt: July 2, 2010

Our Reference Number: NDA 201280

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 **August 31, 2010** 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.

Please note that you are 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). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been

met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

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) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Consumer Safety Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

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/s/

RAYMOND S CHIANG
07/28/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
DMEP (510) Raymond Chiang/WO B.22 Rm 3375/6-1940

REQUEST DATE
7.28.10

IND NO.

NDA/BLA NO.
201280

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG
Ondero (Linagliptin tablets)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Treatment of type 2 diabetes (DPP-4 inhibitor)

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
2.26.11 (assuming substantially complete PI available)

NAME OF FIRM:
Boehringer Ingelheim, Inc.

PDUFA Date: 5.2.11

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

The network location is : <\\CDSESUB1\EVSPROD\NDA201280\201280.ENX>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]
Labeling Meetings: [Insert Dates] TBD (DDMAC will be invited)
Wrap-Up Meeting: [Insert Date] TBD (DDMAC will be invited)

SIGNATURE OF REQUESTER
Raymond Chiang (see detailed information listed above)

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

	<input type="checkbox"/> MAIL	<input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

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

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/s/

RAYMOND S CHIANG
07/27/2010

	<input type="checkbox"/> MAIL	<input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

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

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/s/

RAYMOND S CHIANG
07/27/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 26, 2010
From: Raymond Chiang, Regulatory Project Manager
Subject: FDA request for clinical site information associated with NDA 201280

From: Chiang, Raymond
Sent: Monday, July 26, 2010 2:44 PM
To: 'maureen.oakes@boehringer-ingelheim.com'
Subject: RE: Information request NDA201280 (linagliptin)

That would be fine.
thanks,
ray

From: maureen.oakes@boehringer-ingelheim.com [mailto:maureen.oakes@boehringer-ingelheim.com]
Sent: Monday, July 26, 2010 2:09 PM
To: Chiang, Raymond
Subject: RE: Information request NDA201280 (linagliptin)

Dear Raymond:

The program linagliptin program consists of 4 pivotal studies (1218.15, 1218.16, 1218.17 and 1218.18). The remainder of the studies are considered supportive. There are no ongoing pivotal studies. If acceptable to you, we will provide you with the requested information for these four studies by Monday, August 2nd. Please confirm that this is the information which you are seeking. Many thanks. Maureen

Maureen Oakes, Pharm.D.
Sr. Associate Director
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
Telephone: 203.798.5723
Email: maureen.oakes@boehringer-ingelheim.com

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

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Monday, July 26, 2010 1:30 PM
To: Oakes,Dr.,Maureen DRA BIP-US-R
Subject: RE: Information request NDA201280 (linagliptin)
Importance: High

Maureen,

This is only for the PIVOTAL studies. For on-going studies, please provide the most up-to-date information and/or the information that will be consistent with the NDA submission date cut offs that were utilized.

Again, as a reminder, please provide this information by email and as an amendment to the NDA.

thanks!
ray

From: maureen.oakes@boehringer-ingenelheim.com [mailto:maureen.oakes@boehringer-ingenelheim.com]
Sent: Monday, July 26, 2010 11:57 AM
To: Chiang, Raymond
Subject: RE: Information request NDA201280 (linagliptin)

Dear Raymond:

I am confirming receipt of the email below. Would you kindly clarify which studies you would like included in this response? Is it all phase II and III studies within the NDA? Also, how would you like on-going studies handled? Thank you. Maureen

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

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Monday, July 26, 2010 11:40 AM
To: Oakes,Dr.,Maureen DRA BIP-US-R
Subject: RE: Information request NDA201280 (linagliptin)
Importance: High

From: Chiang, Raymond
Sent: Monday, July 26, 2010 11:37 AM
To: 'maureen.oakes@boehringer-ingenelheim.com'
Subject: RE: Information request NDA201280 (linagliptin)
Importance: High

Maureen,

Please see information request (in black font) from the medical officer concerning NDA 201280 (linagliptin):

Please send a **table** that is organized by the following:

Site number
Principle investigator
Location: city, state, country

The table should contain the following information:

Number of subjects screened
Number of subjects randomized
Number of subjects prematurely discontinued due to adverse events (AEs)
Deaths
Number of Serious AEs

Mean HbA1c efficacy results

Please send this information (by email and as an amendment to the NDA) within a week. Please confirm receipt of this email.

thanks,

ray

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

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/s/

RAYMOND S CHIANG
08/02/2010

From: [Hai, Mehreen](#)
To: ["maureen.oakes@boehringer-ingelheim.com";](mailto:maureen.oakes@boehringer-ingelheim.com)
Subject: RE: IND 70,963-Linagliptin-pre-NDA meeting
Date: Tuesday, December 01, 2009 9:57:15 AM
Attachments: PRELIMINARY MTG RESPONSES IND 70963.pdf

Hi Maureen,
Please find attached our pre-meeting response for the meeting tomorrow. Please confirm that you received it and were able to open it.

After you have had a chance to review the document, please let me know if there are any questions/comments that you think do not need further discussion or that you wish to focus on during the meeting.

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

FDA PRELIMINARY RESPONSES SENT TO BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC. ON DECEMBER 1, 2009

APPLICATION: IND 70,963

DRUG PRODUCT: LINAGLIPTIN (BI 1356) TABLETS

MEETING TYPE: TYPE B, PRE-NDA

INDUSTRY MEETING DATE: DECEMBER 2, 2009

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 December 2, 2009, at 1:00 – 2:00 PM between Boehringer Ingelheim Pharmaceuticals, Inc. 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.

Enclosure: NDA Submission Recommendations

Sponsor's Questions and FDA's Preliminary Responses

CLINICAL

Question 1: Does the Division have any comments on the proposed contents of Module 5?

FDA Preliminary Response: Module 5 appears to be comprehensive. We may have additional requests at the time of or after submission of your New Drug Application (NDA).

Question 2: Does the Division have any comments regarding BI's proposal for the structure and proposed content of the SCE?

FDA Preliminary Response: In your Table of Contents (TOC) under 3.2, where efficacy groups are listed, you have not included section subheadings for various endpoint analyses (i.e. HgbA1c, fasting glucose, HOMA parameters, etc). Please list these under each efficacy group so that it is clear which analyses were done for each group and also so that the results can be readily found. You should also include a section with tables and text for efficacy results in cases of renal impairment in your TOC and the corresponding part of the SCE.

Question 3: Does the Division have any comments regarding BI's proposal for the structure and proposed content of the SCS and safety package?

FDA Preliminary Response: You propose to include hypoglycemia, renal events, hepatic events and hypersensitivities as adverse events of special interest. Linagliptin is a DPP-4 inhibitor and we have emerging concerns regarding pancreatitis and cutaneous skin lesions in this class of drugs. Please also include these two events in your analyses for adverse events of special interest.

In addition, your SCS TOC and corresponding text should include

- Analyses of events by system organ class (SOC) according to the MedDRA classification
- Analyses of serious adverse events (SAEs) that lead to study discontinuation
- Analyses of ECG changes/results

Of note, your cardiovascular analysis as described on page 40 of your SCS states that meta-analysis was performed on Phase III studies only. In your earlier submission describing your plans to address the cardiovascular risks of linagliptin through a meta-analysis, you had proposed also including 12-week Phase II studies. We had responded that 12-week studies would likely add little value to the meta-analysis due to the short exposure and likely very limited number of events. Please clarify why the proposed meta-analysis is limited to Phase III studies and does not include Phase II studies with duration longer than 12 weeks.

In addition, we had recommended inclusion of unstable angina as an endpoint only if hospitalization was required. You mention unstable angina alone as an endpoint. Please clarify and justify your decision.

Question 4: BI proposes to include case report forms (CRFs) for all randomized patients who died during any of the linagliptin clinical trials. In addition, we propose to include CRFs for all patients who discontinued the study due to an adverse event in any of the following Phase III studies: 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, 1218.40 and 1218.50. (Please refer to Table 9:1 in Section 9 of this document for additional information on these studies.)

Does the Division agree with this approach?

FDA Preliminary Response: Yes, we concur. However, we may request additional information at the time of or after the NDA submission.

Question 5: BI proposes to include case narratives (as CIOMS forms) for all randomized patients who died during any of the linagliptin clinical trials. In addition, BI intends to provide case narratives for patients who have discontinued the study due to an adverse event in the

following linagliptin clinical trials: 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, 1218.40, 1218.50. (Please refer to Table 9:1 in Section 9 of this document for additional information on these studies.)

Does the Division concur with the proposed approach?

FDA Preliminary Response: Yes, we concur. However, we may request additional information at the time of or after the NDA submission.

Question 6: Does FDA have any comments to the proposed safety package proposed to be submitted to the 4 month safety update?

FDA Preliminary Response:

- **You propose to include interim data from two studies in renally impaired patients (1218.43 and 1218.64) at the 4-month safety update but not at the time of NDA filing. The pharmacokinetic study of renally impaired nondiabetic patients is therefore the only data in renal impairment that you will provide at the time of filing. Although renal excretion is a minor elimination pathway for linagliptin, we are concerned about off-target DPP-4 inhibition effects on kidney function and that patients with renal impairment may be prescribed linagliptin without supportive safety data. Please plan to provide at least 12 weeks of data in Type 2 diabetic patients with mild and moderate renal impairment at the time of NDA filing. Please clarify how you can achieve this goal and the numbers of patients and type of impairment that will be studied and submitted with the NDA filing.**
- **You have stated that study 1218.20 will be a pivotal efficacy study for linagliptin and have also included this in your 4-month safety update list. Please confirm that 52 weeks of data and results will be submitted at the time of NDA filing. We cannot commit to reviewing any new evidence to support efficacy submitted with the 4-month safety update.**

- **Please clarify the proposed number of patients that will have had exposure to the study drug at the time of NDA filing and the proposed patient exposure that will be submitted with the 4-month safety update.**

Question 7: BI proposes that that all supportive listings, tables and figures for the SCE (Module 2.7.3) will be placed in Module 5.3.5.3, and that these documents (SCE and supportive documentation in 5.3.5.3) fulfill the requirements of the Integrated Summary of Effectiveness (ISE). Similarly, Module 2.7.4, Summary of Clinical Safety, is proposed to fulfill the requirements of the text portion of the Integrated Summary of Safety (ISS), and supportive listings, tables, and figures will be placed in Module 5.3.5.3.

a. Does the Division agree to this approach for the ISE?

FDA Preliminary Response: Yes, we concur. Please also see our comments regarding your SCE (Question 2). We may request additional information at the time of or after your NDA filing.

b. Does the Division agree to this approach for the ISS?

FDA Preliminary Response: Yes, we concur. Please also see our comments regarding your SCE (Question 2). We may request additional information at the time of or after your NDA filing.

Question 8:

a. Does the Agency have any comments to the proposed statistical analysis plans?

FDA Preliminary Response: For treat-to-target response (i.e., HbA_{1c} < 7.0%), we recommend using the FAS population which includes patients having baseline HbA_{1c} < 7.0%.

Please clarify whether the consistency of efficacy in subgroups will be performed for individual studies.

b. Specifically, does the Agency have any comments to the proposed analyses for the use of rescue therapy?

FDA Preliminary Response: Your proposal appears to be acceptable.

Question 9: Does the Division have any comments on BI's proposed to submit the interim analysis of Study 1218.43 with the 4-month safety update?

FDA Preliminary Response: Please see our response to Question 6.

Question 10: Does the Division have any further comment on BI's plans for the submission of clinical data to the NDA?

FDA Preliminary Response: Please see the attached agency recommendations on data presentation for your NDA submission.

NONCLINICAL

Question 11: Appendix 6 outlines the study reports planned to be submitted in Module 4 of the NDA. Does the Division have any comments on the proposed contents of Module 4?

FDA Preliminary Response: 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.**
- **Final carcinogenicity study reports are required at the time of NDA submission, complete with dataset files suitable for FDA Biometrics review. For more information on submitting electronic carcinogenicity data, please contact Karl Lin at karl.lin@fda.hhs.gov.**
- **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.**
- **Nonclinical studies in PDF file format rather than scanned images of the data are preferred.**
- **We note several study reports in your eCTD draft Module 4 Table of Contents may be more appropriate in different sections. Specific suggestions (non-inclusive) include: the acute dermal irritation/corrosion study (#U06-1229) could be moved from Section 4.2.3.1 to 4.2.3.6 and reproductive and developmental toxicity studies in Section 4.2.3.5 have not been allocated by study type.**

CHEMISTRY MANUFACTURING AND CONTROLS

Question 12: Does FDA have any comments to BI's proposed submission strategy?

FDA Preliminary Response: As discussed in FDA's Guideline for Drug Master Files, a Drug Master File (DMF) is "created to allow a party other than the holder of the DMF to reference material without disclosing to that the contents of the file", and "When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF." Therefore, we strongly recommend that you submit the CMC information on the drug substance in your NDA instead of creating a new DMF of which you would be the holder. If a DMF will be cross-referenced for the drug substance information, the following information will be expected in the NDA: authorized reference to the DMF, a brief section on the general properties of the drug substance, regulatory specifications of the drug substance, retest period, and a list of all manufacturing and testing facilities with a readiness statement for FDA's GMP inspections.

Question 13: Does FDA have any comments about the general organization and/or proposed content to be included in Module 3 of the DMF and the NDA?

FDA Preliminary Response: We remind you to provide the following in the NDA: (1) A confirmation that the manufacturing and testing facilities listed in Form FDA 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and that they are ready for inspection; and (2) 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.

Question 14: Does FDA agree that submission of the executed batch record for one primary stability batch for the strength to be marketed is sufficient for review?

FDA Preliminary Response: Yes, we agree that the executed batch record for one primary stability batch will be sufficient.

Question 15: Does FDA agree with the proposed strategy for formatting the methods validation package?

FDA Preliminary Response: Current technology at FDA does not allow easy access to electronic information from outside of CDER. You should provide a methods validation package with all the required information in one location, in section m3.2.r-Regional Information, so that it can be forwarded to FDA's field facilities.

ADMINISTRATIVE

Question 16: Does the Agency have any preliminary comments on BI's proposed approach for investigating the use of linagliptin in the Type 2 pediatric population?

FDA Preliminary Response:

- Your request for a waiver and deferral must be submitted at the time of NDA submission.

- You have stated that you plan to ask for deferral in patients (b) (4) years of age, but you plan to study linagliptin in patients 10 years of age to (b) (4) years. Please explain why you would request a pediatric deferral starting at age (b) (4) if you plan to study ages down to 10 years.
- We recommend that you conduct a dose-ranging trial in pediatric patients, including additional doses other than the proposed 1 mg and 5 mg, to characterize the pharmacokinetics and pharmacodynamics. The information from this study will aid in optimizing the pediatric dosing in your efficacy and safety trial.

Question 17: The linagliptin NDA is planned to be submitted as an eCTD. The briefing package includes an electronic submissions proposal (Appendix 10), describing technical aspects of the submission, including identification of analysis datasets planned to be included in the NDA.

- (a) Does the FDA have any comments to this proposal, including comments on the:
- analysis datasets proposed to be included (Section 4.1)?
 - 4-month safety update (Section 5)

FDA Preliminary Response: The proposed analysis datasets are not review ready and will not permit an adequate review. We view this as a filing issue and failure to correct this deficiency will result in a refusal-to-file. For general format and structure, please use CDISC/ADaM (<http://www.cdisc.org/adam>) standards. Please also refer to the analysis dataset section of the Study Data Specifications document (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Please submit analysis datasets for studies 1218.5 and 1218.6. Also see our response to Question 6.

- (b) BI does not intend to submit pharmacokinetic datasets as part of the eCTD. These data are available upon request. Does the Division agree that these data are not necessary for review of the planned NDA?

FDA Preliminary Response: You should submit the pharmacokinetic (PK) data sets for any pivotal PK trials including those that support the labeling information.

Question 18: Does the Agency concur that the provided list includes all studies requiring disclosure of financial arrangements between the sponsor and the investigator of these covered studies for the purpose of the linagliptin NDA?

FDA Preliminary Response: Yes, we concur.

Attachment 1

General CLINICAL Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Section 7.4.2 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.4.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.4.2 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.4.3 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.4.3 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.4.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.4.4 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.4.4. – Standard analyses and explorations of ECG data.
12. Section 7.6.4 – Overdose experience.
13. Section 7.5.1 - Explorations for dose dependency for adverse findings.
14. Section 7.5.2 - Explorations for time dependency for adverse findings.
15. Section 7.5.3 - Explorations for drug-demographic interactions.
16. Section 7.5.4 - Explorations for drug-disease interactions.
17. Section 7.5.5 - Explorations for drug-drug interactions.

18. Section 7.5.5 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, please include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)
8. Financial disclosure information for each investigator

Common PLR Labeling Deficiencies

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].
[See 21 CFR 201.57(a)(1)]

4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
8. Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
11. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
12. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

13. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

15. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19. When a subsection is omitted, the numbering does not change.
20. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
24. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
33. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
34. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

CDISC Data Requests to Sponsors Quantitative Safety and Pharmacoepidemiology Group

Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- b. Safety endpoints for Adverse Events of Special Interest (AERI)
- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
 - a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - (DV) Protocol deviations
 - (DA) Drug Accountability
 - (PC, PP) Pharmacokinetics
 - (MB, MS) Microbiology

- (CF) Clinical Findings
 - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - Tumor information
 - Imaging Data
 - Complex Inclusion/Exclusion Criteria
3. Variables
- a. All required variables are to be included.
 - b. All expected variables should be included in all SDTM datasets.
 - c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
 - d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
 - e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
 - f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
4. Specific issues of note:
- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
 - b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
 - c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues

1. Please specify which ADaM datasets you intend to submit.
2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.

3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
5. Please indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items

Controlled terminology issues

- a. Please use a single version of MedDRA for a submission. Does not have to be most recent version
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Please refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements should be addressed.

Additional FDA Comments

The Division requests the following for the submitted datasets:

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that should include the following fields/variables:

- a. A unique patient identifier
 - b. Study/protocol number
 - c. Patient's treatment assignment
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)
 - g. Duration of event (or start and stop dates)
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
 - m. Whether the event was a new condition or an exacerbation of an existing condition.
2. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form. Also provide the conventions used to map to the MedDRA terms.
 3. Please see the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.

4. In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Please provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Please perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. Also, for the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format.
11. Please perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. In every dataset, all dates should be formatted as ISO date format.
13. Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or

- "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.
14. All datasets should contain the following variables/fields (in the same format and coding):
 - a. Each subject should have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
 15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
 16. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events, and individuals who had an AE within 30 days of discontinuation.
 17. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
 18. With reference to the table on the following page, please note that the HLG and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-70963

GI-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

Linagliptin (BI 1356) Tablets.

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

/s/

MEHREEN HAI
12/01/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 70,963

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Kathryn M. Jason, Ph.D.
Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Jason:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BI 1356 Tablets.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on December 11, 2007. The purpose of the meeting was to discuss available data and your plans for additional studies to support a New Drug Application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from End-of-Phase 2 meeting held on December 11, 2007.

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 11, 2007
TIME: 1:00 – 2:00 P.M.
LOCATION: White Oak Campus, Silver Spring, MD
APPLICATION: IND 70,963
DRUG NAME: BI 1356 Tablets
TYPE OF MEETING: End-of-Phase 2; Type B
MEETING CHAIR: Mary Parks, MD
MEETING RECORDER: Julie Marchick, MPH

FDA ATTENDEES:*Division of Metabolism and Endocrinology Products:*

Mary Parks, MD	Director
Hylton Joffe, MD, MMSc	Acting Diabetes Clinical Team Leader
Todd Bourcier, PhD	Pharmacology/Toxicology Team Leader
David Carlson, PhD	Pharmacology/Toxicology Reviewer
Julie Marchick, MPH	Regulatory Project Manager

Office of Biostatistics:

J. Todd Sahlroot, PhD	Biostatistics Team Leader
Lee Ping Pian, PhD	Biostatistics Reviewer

Office of Clinical Pharmacology:

Sally Choe, PhD	Clinical Pharmacology Team Leader
Sang Chung, PhD	Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Holger Fuchs, Ph.D.	Preclinical Pharmacokineticist
Arno Kalkuhl, Ph.D.	Toxicologist
Anette Brunner-Schwarz, Ph.D.	R & D Project Leader
Hans-Guenter Schaefer, Ph.D.	Head, Clinical Pharmacokinetics Group
Arne Ring, Ph.D.	Statistician, Phase 2 Studies
Dietmar Neubacher, Dipl. Stat.	Statistician, Phase 3 Studies
Hans-Juergen Woerle, M.D.	Team Member Medicine
Leo Seman, M.D., Ph.D.	Director, Clinical Research
Klaus Dugi, M.D.	VP, Medical Therapeutic Area Head
Paul Bispham, Ph.D.	Drug Regulatory Affairs Team Leader
Kathryn Jason, Ph.D.	Director, Drug Regulatory Affairs
Christopher Corsico, M.D.	VP, Drug Regulatory Affairs
Thor Voigt, M.D.	Sr. VP, Medical And Drug Regulatory Affairs
Mathias Senger, Ph.D.	International Project Leader

BACKGROUND:

IND 70,963 for BI 1356 tablets was submitted by Boehringer Ingelheim Pharmaceuticals, Inc. on August 19, 2005. BI 1356 is a dipeptidyl peptidase IV (DPP-IV) inhibitor being developed for the treatment of type 2 diabetes mellitus (T2DM).

Proposed Phase 3 Clinical Program

Protocol 1218.15 - *A randomized, double-blind, placebo-controlled, parallel group 24 week study to assess the efficacy and safety of BI1356 5 mg in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug naïve or previously treated type 2 diabetic patients with insufficient glycaemic control*

Protocol 1218.16 – *A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycaemic control*

Protocol 1218.17 – *A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy*

Protocol 1218.18 – *A randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 1356 (5 mg), administered orally, once daily over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea*

Protocol 1218.20 – *A randomized, double-blind, active controlled parallel group efficacy and safety study of BI 1356 (5.0 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy*

Protocol 1218.35 – *A randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 1356 (5 mg), administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite a therapy with a sulphylurea drug*

Protocol 1218.50 – *A randomized, double-blind, placebo-controlled, parallel group efficacy and safety study of BI 1356 (5 mg), administered orally once daily for 18 weeks followed by a 34 week double-blind extension period (placebo patients switched to glimepiride) in type 2 diabetic patients with insufficient glycemic control for whom metformin therapy is inappropriate (intolerability or contraindication)*

MEETING OBJECTIVES:

To discuss available data and plans for additional studies to support a New Drug Application (NDA) for BI 1356 for the treatment of type 2 diabetes.

DISCUSSION POINTS:

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's responses provided to the Sponsor on December 10, 2007, follow in bold font. A summary of the meeting discussion is in italics.

Question 1.1

The core Phase III protocol, and synopses of the studies to be carried out to assess safety and efficacy of BI 1356 are presented in Item 9 (see Attachments 9-1 and 9-2).

Is the proposed clinical development plan adequate to support the following indication statements?

- BI 1356 is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.



Division Response: The Division is no longer issuing separate indications for specific combinations of drugs and biologics for the treatment of type 2 diabetes. The indication section in labeling is instead being replaced by a single, simplified indication (Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus). If the risk/benefit profile is favorable when the Sponsor's drug is used in combination with other drugs, the study findings and conclusions will be described in the Clinical Studies section of the label, effectively providing support for the combination use in clinical practice. If BI 1356 is not studied in combination with anti-hyperglycemic medications that are likely to be commonly co-administered with BI 1356 in clinical practice, the Division will require that the label contain a statement reflecting this limitation under "Important Limitations of Use".

Question 1.2

For this product and indication, does the Division concur that it is appropriate to request a deferral, under 21 CFR 314.55, of the requirements for pediatric studies in patients ^{(b) (4)} years old, and a waiver of the requirements for studies of pediatric patients under ^{(b) (4)} years old?

Division Response: This question is premature. If the Sponsor wishes to obtain a deferral or waiver for postmarketing pediatric studies, the Sponsor should submit a formal request with justification at the time of the NDA submission.

Nonclinical Question

Question 2.1

BI has carried out chronic toxicology studies in primates, as summarized in the enclosed Investigator's Brochure (Attachment 9-3). The final draft report of the 52-week study is included in this IND, submitted as Serial No. 0026/ October 18, 2007, and Serial No. 0019/ October 19, 2007). Does the agency concur that the completed preclinical testing for cutaneous lesions in primates is adequate based on current knowledge?

Division Response: Yes.

Biopharmaceutics and Clinical Pharmacology Question

Question 3.1

Do you concur that the data available, and completion of the planned studies (See Attachment 9-4), will provide a data package that adequately addresses Biopharmaceutics and Clinical Pharmacology for BI 1356?

Division Response: Yes. However, the Division is concerned about interpreting the extrinsic effects (e.g., food effect and drug interaction) on BI 1356 because the change in systemic exposure to BI 1356 may not be a sensitive measure for the effect of extrinsic factors on BI 1356 due to the non-linear pharmacokinetic properties of BI 1356. Therefore, the typical bioequivalence criteria of 20% change might not be applicable in assessing the extrinsic effects on BI 1356. The Sponsor is asked to justify their approach applying the bioequivalence criteria to the evaluation of extrinsic effect studies.

The Division recommends that the Sponsor use glycemic parameters (i.e., fasting plasma and/or HbA1c) in addition to DPP-4 inhibition as PD parameters for PK-PD modeling.

Meeting Discussion: The Division agreed to provide a reference in the meeting minutes (see attachment) that illustrates a potential approach for assessing bioequivalence when a drug has a non-linear dose-response relationship. The Division will consider the Sponsor's own approach if submitted with adequate scientific justification.

Clinical Questions

Question 4.1

Safety data for BI 1356 are included in the IB (Attachment 9-3), the Safety Analysis of BI 1356 (Attachment 9-5), and with the Data Summaries of Phase II studies 1218.5 and 1218.6 (Attachment 9-6). Do you concur that data available indicate that it is sufficiently safe to proceed into Phase 3 studies of BI 1356, including long-term open label studies?

Division Response: Yes.

Question 4.2

Does the FDA concur with the dose selection for Phase 3 studies, as presented in Attachment 9-7?

Division Response: No. In the Sponsor's 12-week monotherapy phase 2 study (1218.5), the 2.5 mg and 5 mg doses of BI 1356 had similar efficacy. The Division recommends that the Sponsor obtain more experience with the 2.5 mg dose in some of the phase 3 clinical trials. The rationale for this recommendation stems from the Division's experience with other products in which long-term data were only obtained for one dose in phase 3. For some of these products, safety issues unforeseen during phase 2 emerged that resulted in an unfavorable benefit:risk balance, preventing approvability of the only dose adequately studied in phase 3.

Question 4.3

Does the FDA concur with the primary statistical analysis proposed for the Phase 3 trials presented in Attachment 9-8, and in section 7 of the core Phase III protocol?

Division Response:

- 1. Randomization is stratified by HbA1c at the beginning of the placebo run-in period (HbA1c <8.5% or ≥8.5%) and prior oral antidiabetic (OAD) use (none, mono, or combination therapy).**

Therefore, for the ANCOVA model for the primary analysis, the Sponsor should consider putting the HbA1c strata as well as OAD use as a fixed effect in the model.

Meeting Discussion: The Sponsor has decided to use continuous HbA1c as a covariate in the model which is acceptable to the Agency

- 2. The Sponsor plans to explore the effect of center and treatment-by-center interaction in the model. The center size is small (4 to 6 patients), therefore, the Sponsor should consider using country or region.**

Meeting Discussion: The Agency referred the Sponsor to the Guidance for Industry: E9 Statistical Principles for Clinical Trials, which recommends not including center in the model if there are a large number of centers, and stated that it would be preferable to use region instead. The Sponsor will be providing descriptive/graphical data by region or center. The Sponsor will also be testing for interactions in a secondary model.

- 3. For sensitivity analysis, the Sponsor should consider performing the Full Analysis Set (FAS)-completers analysis instead of per protocol analysis.**
- 4. Concerning the 0.35% noninferiority margin in the trial comparing BI 1356 and glimepiride, the Sponsor should use a proportion (e.g. 50%) of the lower bound of the 95% confidence interval of the estimated effect size across historical trials comparing glimepiride and placebo to calculate the margin. In addition, the Sponsor is asked to provide a clinical justification for the margin.**

Meeting Discussion: The Agency clarified that the estimated effect size comparing glimepiride and placebo should be calculated by performing a meta-analysis of similar historical trials. The Sponsor stated that this is reasonable.

- 5. The 52-week unblinded exploratory interim analysis of the 104-week glimepiride controlled, add on to metformin trial is intended for regulatory purposes and is not planned to test a specific confirmatory hypothesis but rather to present a 95% confidence interval for the difference between BI 1356 and glimepiride. To maintain the integrity of the trial, the Sponsor should not perform an unblinded interim analysis on efficacy variables but keep the blind for the efficacy outcome variables until the end of the study hypothesis testing at Week 104.**

Meeting Discussion: The Sponsor stated that investigators will stay blinded. The Sponsor stated that they would delay submission of the NDA to have the 12- and 18- month data available at the time of filing. The Agency stated that this is acceptable, but inquired whether the primary efficacy time point could be changed from 2-year to 1-year. The Sponsor stated that they want to analyze the primary efficacy variable at 2 years and plan to request inclusion of both 1-year and 2-year efficacy data in the label.

Post-meeting comment: The Sponsor does not need to adjust for multiplicity when analyzing both the 1-year and 2-year efficacy data, provided that the 1-year efficacy results are not used for decision-making (e.g., whether to continue the trial). With regard to efficacy, only the primary timepoint data (currently the 2-year data) can be included in the label. If the Sponsor wants to include both 1-year and 2-year efficacy data in the label, there should be adjustment for multiplicity and both these timepoints should be listed as co-primary timepoints. Regardless, all currently enrolled participants in this trial should have at least 12-months of safety data available at the time of NDA submission.

6. The Sponsor did not provide plans for the subgroup analyses on gender, race, age group and renal function.

Pooling data across studies on renal function subgroup might require a prespecified meta-analysis plan since the randomization ratios among studies for placebo/active drug and BI 1356 are 1:1, 1:2, or 1:3.

Meeting Discussion: The Agency referred the Sponsor to the Guidance for Industry: E9 Statistical Principles for Clinical Trials for guidance on how to analyze and present the results of subgroup analyses in the NDA. The Division stated that there is no need for the Sponsor to submit additional information on the proposed subgroup analyses prior to the NDA submission.

Question 4.4

Are the safety assessments in the proposed Phase III development plan adequate to evaluate safety in the target population (see core Phase III protocol and BI 1356 Safety Summary in Attachments 9-1 and 9-5)?

Division Response: Based on emerging safety signals with other DPP-IV inhibitors, the Sponsor should prespecify liver test abnormalities (reference to the draft *Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation*) and hypersensitivity reactions (e.g., angioedema, angioedema-like events, and anaphylaxis) as adverse events of interest and ensure that these events are adequately captured in the Sponsor's clinical trials and appropriately analyzed for the NDA. In addition, the Sponsor should specify renal safety as an adverse event of interest, because BI 1356 is concentrated in the kidney in the Sponsor's non-clinical studies and causes toxic renal effects, albeit at high exposures.

Question 4.5

The Phase III clinical development program will include patients with mild and moderate renal insufficiency, and a kinetic/safety study in volunteers with renal insufficiency will be carried out (See Attachments 9-1, 9-2, and 9-5).

Do you concur that, based on the drug profile of BI 1356, the data proposed to be obtained from the program will be sufficient to assess safety of BI 1356 inpatient with renal insufficiency?

Division Response: Renal insufficiency is a common complication of longstanding diabetes; therefore, many patients with renal impairment may receive BI 1356, if approved. Januvia, the only FDA-approved DPP-IV inhibitor causes small increases in serum creatinine among patients with moderate renal insufficiency (Januvia label) and the Division does not yet know if this is a DPP-IV inhibitor class-effect. Based on these reasons, it is important that the efficacy and safety of BI 1356 be evaluated in patients with renal insufficiency. The Sponsor's proposed pharmacokinetic study in volunteers with renal insufficiency seems reasonable. The Sponsor estimates that there will be 300-500

patients with mild renal impairment and 100-300 patients with moderate renal impairment in the phase 3 program. Prior to the face-to-face meeting (or, if that is not possible, at the face-to-face meeting), the Sponsor is asked show how these exposures to BI 1356 (numbers of patients and duration of exposure) will be distributed across the phase 3 trials that will be included in the NDA. Because the Sponsor's phase 3 program will only include 5-15 patients with severe renal impairment, the Division requires that the Sponsor complete a dedicated renal safety study in patients with severe renal impairment.

Meeting Discussion: The Division reiterated the importance of studying BI 1356 in renally impaired patients with diabetes. The Sponsor presented slides showing the expected exposures to BI 1356 in patients with renal insufficiency included in the phase 3 trials (see attachment). The Sponsor anticipates having BI 1356 exposure data on 255-425 patients with mild renal impairment, 85-255 patients with moderate renal impairment, and <20 patients with severe renal impairment in the clinical trials. The Division stated that the proposed numbers of patients with mild and moderate renal insufficiency are reasonable, but stressed the importance of these patients having sufficient long-term exposure to BI 1356. The Division also reiterated the need for a dedicated renal safety study in patients with severe renal impairment because the phase 3 trials will include few patients with severe renal impairment.

The Division and Sponsor may need to revisit the need for a dedicated study in patients with mild and moderate renal impairment if the actual numbers of these patients in the phase 3 trials are substantially lower than the anticipated sample sizes described above.

The Sponsor asked for a definition of severe renal impairment. The Division stated that the Cockcroft-Gault formula is usually used, and this category is defined as having a glomerular filtration rate (GFR) < 30 mL/min. The Division offered to review the protocol of a dedicated renal impairment study if the Sponsor submits the protocol with questions and a request for comments. The Division requests that the data from the renal impairment study ideally be available at the time of NDA filing. If the data are not available at that time, the data will likely be required as a Phase 4 commitment – in this case, the Sponsor should provide justification in the NDA for not providing the data pre-approval.

Question 4.6

Do you concur that the cardiac electrophysiology data available and data we propose to collect from Phase III studies and the planned QT c study (Protocol in Attachment 9-1), will be adequate to address the effect of BI 1356 on cardiac repolarization?

Division Response: The Sponsor's QT study protocol will be submitted to the Agency's Interdisciplinary Review Team (IRT) for review upon receipt of the Highlights of Clinical Pharmacology Table, requested on December 6, 2007.

Question 4.7

Does the FDA concur with BI's plans to conduct a limited safety study of 12 weeks treatment duration (e.g. in 100-200 patients) of the combination of BI 1356 with insulin post marketing?

Division Response: This question is premature and the Division's response will depend upon our findings of efficacy and safety in the NDA. However, the Division notes that 12 weeks is shorter than typically seen for add-on to insulin studies and that the Sponsor's proposed sample sizes may be too small.

Meeting Discussion: The Sponsor clarified that the main purpose of this question was to obtain input from the Division as to whether the add-on to insulin study can be conducted post-approval instead of pre-approval. The Division stated that the proposal to study the combination of BI 1356 with insulin as a Post Marketing Commitment is reasonable.

Question 4.8

Is the proposed extent of patient exposure in the clinical program, as described in the Safety Analysis (Attachment 9-5) adequate to support registration?

Division Response: The Division is unable to answer this question based on the information included in the briefing package. Prior to the face-to-face meeting (or, if that is not possible, at the face-to-face meeting), the Sponsor is asked to show the duration of exposure to BI 1356 (number of patients with exposure to BI 1356 ≥ 6 months, ≥ 12 months, ≥ 18 months, ≥ 24 months) for each of the phase 3 trials that will be included in the NDA.

Meeting Discussion: The Sponsor provided slides showing expected patient exposures to BI 1356 at the time of NDA submission and at the time of the 4 month safety update for each of the phase 3 trials to be included in the NDA (see attachment). The Division stated that the proposed exposures at the time of NDA submission are too low to support a complete registration package (6-month data for only ~1,500 BI 1356-treated patients and 12-month data for less than 500 BI 1356-treated patients). Furthermore, according to the Sponsor's proposal, the Division noted that the 6-month exposure data will be doubled and the 12-month exposure data will be tripled at the time of the 4-month safety update compared to the data available at the time of NDA submission. Based on these observations, the Division expressed concern with the Sponsor's plan to submit a lot of new data at the time of the 4 month safety update. The Division stated that the 6-month ($n \sim 3,000$), 12-month ($n \sim 1,250$), and 18-month ($n \sim 300-400$) exposures to BI 1356 currently proposed at the time of the 4-month safety update be present at the time of NDA submission to support a complete NDA package.

Other Comments:

1. Hypoglycemia should be defined in all your clinical protocols.
2. For some of the phase 3 trials, the Sponsor proposes a six-week washout of prior anti-hyperglycemic therapy. The Sponsor is asked to justify this duration of washout, as changes in glycemic control will take 2-3 months to be fully reflected in the baseline HbA1c measurement. Also, the washout for prior thiazolidinedione therapy should be at least eight weeks.

3. **The Sponsor's proposed glycemic rescue criteria (page 32 of the "Core Protocol Phase III Studies" section) should be modified to become more stringent as the trial progresses. For example, the Sponsor could require glycemic rescue if**
 - Fasting plasma glucose (FPG) >240 mg/dL up to Week 12**
 - FPG >200 mg/dL after Week 12**
 - HbA1c >8.5% after Week 24**
4. **For the combination therapy trials, the Sponsor should specify in the protocols that patients must have inadequate glycemic control on maximally effective doses of background anti-hyperglycemic therapy (e.g., at least half-maximal doses of sulfonylurea, at least 1,500-2,000 mg of metformin therapy, etc.).**
5. **In the synopsis for Study 1218.35, the title states that study medication will be administered for 24 weeks but the duration of treatment section states that there will be an 18 week double-blind treatment period. The Sponsor is asked to clarify.**
6. **Which of the phase 3 trials will have extensions and will these be controlled or uncontrolled extensions?**

ATTACHMENTS/HANDOUTS:

Slides presented by Sponsor during the meeting

Reference provided by Division – PD Modeling in the Documentation of Bioequivalence

Minutes Preparer: Julie Marchick

Chair Concurrence: Mary Parks

28 Pages have been Withheld in Full as B4
(CCI/TS) Immediately Following this Page

Linked Applications

Sponsor Name

Drug Name

IND 70963

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

BI 1356 BS TABLETS

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

/s/

JULIE C MARCHICK

01/24/2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 201280 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Tradjenta (pending) Established/Proper Name: linagliptin Dosage Form: tablets: 5 mg		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Raymond Chiang		Division: DMEP

NDA:
 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)):

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

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:

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	
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is _____ 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> 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 _____	<input type="checkbox"/> Received

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.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
<p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s)
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7.2.10
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	see most recently approved saxagliptin and sitagliptin package insert labels

³ Fill in blanks with dates of reviews, letters, etc.
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<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7.2.11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Please see most currently approved labels for Onglyza (saxagliptin) and Januvia (sitagliptin).
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	4.8.11; 10.7.10 4.8.11; 10.6.10
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 2.15.11; 4.4.11 <input checked="" type="checkbox"/> DRISK 3.25.11 <input checked="" type="checkbox"/> DDMAC 3.14.11; 3.29.11 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 10.7.10
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>March 16, 2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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 (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	4.6.11; 4.4.11 (2); 4.1.11; 3.24.11; 3.10.11; 3.9.11; 3.8.11; 3.7.11; 2.11.11; 2.10.11; 2.9.11; 2.7.11; 2.4.11; 1.20.11; 1.19.11; 1.14.11; 12.14.10; 12.10.10; 12.8.10; 11.17.10; 11.17.10; 11.3.10; 9.22.10; 9.9.10; 9.8.10; 8.24.10; 8.2.10; 7.26.10
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 12.1.09
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 12.11.07
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None pending
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None pending
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4.4.11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	3.13.11 (sign off of primary review)
• Clinical review(s) (<i>indicate date for each review</i>)	3.11.11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	please see section 3.3 (page 21) of Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.
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❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	OND DDS memo 3.17.11 <input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 2.11.11
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.14.11 (sign off of primary review for CV safety)
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.14.11; 3.11.11 (sign off of primary review); 3.14.11 (sign off of primary review for CV safety)
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.11.11; 3.14.11 (for CV safety)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.9.11 (sign-off of primary review); 3.8.11 (sign-off of primary review); 8.27.11 (sign-off of filing review)
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.7.11; 3.7.11; 8.27.10 (filing review);
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.24.11
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.10.11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3.7.11; 8.12.11 (filing review);
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 2.21.11
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 1.31.11 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality	<input type="checkbox"/> None
<ul style="list-style-type: none"> ✓ Product Quality Discipline Reviews 	
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 3.14.11
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 3.7.11 (sign-off of primary review); 3.1.11 (sign-off of primary biopharm review); 2.2.11 (sign-off of primary review); 10.22.10 (sign-off of QbD review); 8.12.10 (sign-off of primary biopharm review); 8.9.10 (sign-off of primary review)
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 3.7.11, 2.28.11 (biopharm review); 2.2.11; 10.22.10 (QbD review); 8.9.10 (filing review); 8.9.10 Biopharm filing review
<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ~ Environmental Assessment (check one) (original and supplemental applications) 	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> 	see page 197 of CMC review dated 2.2.11
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> 	N/A
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> 	N/A
<ul style="list-style-type: none"> ❖ Facilities Review/Inspection 	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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 sites⁶)</i> 	Date completed: 8.9.10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i> 	Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> 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.

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.