

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204629Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204629

SUPPL #

HFD # 510

Trade Name Jardiance

Generic Name empagliflozin

Applicant Name Boehringer Ingelheim

Approval Date, If Known 8/1/14

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 XX 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 XX 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 XX 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 XX

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 XX

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 XX

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:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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

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

Investigation #1 !
IND # YES ! NO
! Explain:

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

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

interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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: Patricia Madara
Title: Regulatory Project Manager
Date: 7/23/14

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

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

7/28/14

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 204629 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)
Proprietary Name: Jardiance Established/Proper Name: empagliflozin Dosage Form: oral tablet		Applicant: Boehringer Ingelheim Pharmaceuticals Agent for Applicant (if applicable):
RPM: Patrica Madara		Division: DMEP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) <p>Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is 8/3/14 		XX AP <input type="checkbox"/> TA CR
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 		<input type="checkbox"/> None CR 3/4/2014
❖ 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
❖ Application Characteristics ³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

2 ✓

Review priority: Standard Priority
 Chemical classification (new NDAs only): 1 - NME
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR 3/5/14 Approval:
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	XX Included sent to company 7/24/14
• Original applicant-proposed labeling	XX Included 3/5/13
❖ 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 XX Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	3/5/13
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	XX Included ; 2/28/14
✓ Proprietary Name	Acceptable; letter 6/18/14, 7/25/13 Review 6/16/14; 7/25/13 ✓
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	
• Review(s) (<i>indicate date(s)</i>)	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: XX 5/17/13 ✓ DMEPA: 11/25/13 ✓ DMPP/PLT: 7/11/14; 12/20/13 OPDP: 7/16/14; 12/17/13 ✓ SEALD: XX None CSS: XX None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM: 5/17/13 ✓
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	XX Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included ←
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes XX No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<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 XX No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>11/6/13 and 2/12/14</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	included ✓ <i>Do not include previous action letters</i>
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	included ✓
❖ Minutes of Meetings <ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) EOP2 meeting (<i>indicate date of mtg</i>) Mid-cycle Communication (<i>indicate date of mtg</i>) <i>This should be in the communication section</i> Late-cycle Meeting (<i>indicate date of mtg</i>) Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	XX N/A or no mtg <input type="checkbox"/> No mtg 11/27/12 ✓ <input type="checkbox"/> No mtg 5/4/10 ✓ 9/5/13 ✓ 12/2/13 ✓
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> Date(s) of Meeting(s) 	XX No AC meeting ✓
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/4/14 ✓
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/4/14 ✓
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	2/27/14 ✓
PMR/PMC Development Templates (<i>indicate total number</i>)	4 <i>Not in DARRTS yet</i>
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) Clinical review(s) (<i>indicate date for each review</i>) Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	X No separate review 3/31/14 3/31/14 11/5/13; 5/3/13 XX 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>)	Clinical review 11/5/13; pg 25 - 26 ✓
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Oncology 10/17/13; OSE 10/20/13 ✓
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	XX N/A ✓

❖ Risk Management	
<ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<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>) 	<p>none</p> <p>none</p> <p>XX 11/12/13 ✓</p>
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested summary: 3/4/13; letters included ✓
Clinical Microbiology XX None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	XX No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	XX No separate review ✓
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None DB II 10/30/13; 4/29/13 ✓ DB VII 11/1/13; 4/25/13 ✓
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	XX No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	XX No separate review ✓
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/8/13; 5/3/13 ✓
OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	XX None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<p>No separate review 3/4/14 ✓</p> <p><input type="checkbox"/> No separate review 11/7/13 ✓</p> <p><input type="checkbox"/> None 11/5/13; 4/26/13 ✓</p>
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	XX None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 10/15/13 ✓
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 10/3/13 ✓
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	XX None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		X No separate review ✓
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 6/11/14; 3/3/14; 11/6/13, 9/13/13, 4/17/13 ✓ Biopharmaceutics 7/20/14; ✓ 11/4/13 ✓ 4/12/2013 ✓
❖ Microbiology Reviews <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 (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		XX Not needed ✓
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		XX None ✓
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Quality review #1 pg 88
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 6/11/14 ✓ XX Acceptable Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ 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 XX Not needed (per review)

⁵ 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.

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done NA
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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

/s/

PATRICIA J MADARA
08/02/2014

JEAN-MARC P GUETTIER
08/02/2014

From: Madara, Patricia
To: daniel.coleman@boehringer-ingelheim.com
Subject: NDA 204629 - PMR / PMC milestone dates required
Date: Monday, July 07, 2014 4:56:00 PM
Attachments: [2014_7_7_empagliflozin_JARDIANCE_NDA_204-629_PMR_PMC_Language.doc](#)
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jardiance (empagliflozin) tablets, 10 mg and 25 mg. In addition, we reference the June 3, 2014, submission which constituted a complete response to our March 5, 2014, action letter.

We continue to review your application. We have attached a draft list of PMRs / PMCs based on the data and internal analyses available at this time. Please complete the form with milestone dates and return to us by email, on or before July 10, 2014.

Contact me if you have any questions. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

**PMR/PMC list for NDA 204629
JARDIANCE (empagliflozin) tablets**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission**, **Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A single-dose pharmacokinetic and pharmacodynamics study of empagliflozin in pediatric patients 10 to <18 years of age with type 2 diabetes mellitus.

Study Completion:

Final Report Submission:

2. A 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of empagliflozin for the treatment of pediatric patients 10 to <18 years of age with type 2 diabetes mellitus as an add-on to metformin, followed by a 28-week double-blind, placebo- or active-controlled extension period. The efficacy and safety study should have at least 30% of randomized subjects 10 to 14 years of age and at least one-third (but not more than two-thirds) of subjects in both age subsets (10 to 14 years and 15 to <18 years) will be female. Secondary safety endpoints should include the effect of empagliflozin on mineral and bone metabolism, and the effect of empagliflozin on growth. This trial should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

3. A study to evaluate empagliflozin toxicity in juvenile rats.

Study Completion:

Final Report Submission:

4. A randomized, double-blind, placebo-controlled trial evaluating the effect of empagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with empagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of empagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. Estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening renal function.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

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/s/

PATRICIA J MADARA
07/08/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204629

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Daniel T. Coleman, Ph.D.
Sr. Associate Director, Regulatory Affairs

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated and received June 3, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Empagliflozin Tablets, 10 mg and 25 mg.

We also refer to your correspondence, dated and received June 5, 2014, requesting review of your proposed proprietary name, Jardiance.

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

If any of the proposed product characteristics as stated in your June 5, 2014, 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 Lyle Canida, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1637. For any other information regarding this application, contact Patricia Madara, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
06/18/2014

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenheim.com
Subject: NDA 204629 (empagliflozin)
Date: Tuesday, June 17, 2014 1:13:00 PM
Importance: High

NDA 204629

INFORMATION REQUEST

Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review your application and have the following request for information:

- **We reference your proposed juvenile rat study protocol entitled “Juvenile Toxicity Study with Empagliflozin in the Rat”, submitted to us on December 3rd 2013. We note from your cover letter, that the latter rat juvenile toxicity study was due to begin in (b) (4). Please, can you provide us an update of the study status? Specifically, please provide a timeline for study initiation, study completion and final report submission.**

You may submit this information informally, via email but also submit your responses officially to NDA 204629. Contact me if you have any questions.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
06/17/2014



NDA 204629

**ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

We acknowledge receipt on June 3, 2014, of your June 3, 2014, resubmission to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jardiance (empagliflozin) tablets, 10 mg and 25 mg.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is August 3, 2014.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
06/17/2014



NDA 204629
IND 102145

GENERAL ADVICE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) and to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We also refer to your December 20, 2013 (to NDA 204629) and January 22, 2014 (to IND 102145), submissions, containing a revised Pediatric Study Plan (PSP) and proposed change to a pediatric protocol for empagliflozin.

We have reviewed the referenced materials and have the following comments:

(b) (4)

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEAN-MARC P GUETTIER
04/09/2014



NDA 204629

GENERAL ADVICE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated and received March 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We also refer to your March 17, 2014, submission, containing a request for agreement regarding the proposed content of the safety update to be provided when NDA 204629 is resubmitted for review. Your submission contained a single question which is repeated below. Our response follows in **bold** font.

Question

Does the Agency concur with Boehringer Ingelheim's proposal for the safety update as outlined in this letter to support the resubmission of NDA 204629 in 2Q14?

FDA Response

We do not concur with the proposed safety update. (b) (4)

To facilitate review, updated safety information as described in your proposal for melanoma and lung cancer should also be provided for deaths, serious adverse events, and all of the other adverse events of special interest. Analysis by age, gender, and baseline renal function should be performed as appropriate. New information should be clearly delineated from the information submitted with the initial NDA. As discussed in our Complete Response letter issued on March 4, 2014, you should:

- **Present tabulations of the new safety data combined with the original NDA data.**
- **Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.**

Any significant changes to the safety profile or new safety findings that result from analysis of the updated safety information should be described in detail.

If you have any questions, contact Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEAN-MARC P GUETTIER
03/31/2014

**PeRC BPCA/Pediatric Study Plan Subcommittee
Meeting Minutes
February 12, 2014**

PeRC Members Attending:

Lynne Yao
 Rosemary Addy
 Hari Cheryl Sachs
 George Greeley
 Michelle Roth-Cline
 Jane Inglese
 Wiley Chambers
 Tom Smith
 Karen Davis-Bruno
 Shrikant Pagay
 Lily Mulugeta
 Dianne Murphy (Did not review: (b) (4))
 Maura O'Leary
 Gregory Reaman
 Coleen LoCicero
 Peter Starke

BPCA/Initial Pediatric Study Plan

9:00	NDA	(b) (4)		
9:30	IND	(b) (4)		
10:00	NDA	204629	Jardiance (empagliflozin) Deferral/Plan Discussion	Type 2 Diabetes Mellitus
10:20	IND	(b) (4)		
10:50	IND			
11:20	IND			
11:35	IND			
11:45	IND			
	<i>IND</i>			

(b) (4)

Jardiance Deferral/Plan Discussion

- Proposed Indication: Type II Diabetes Mellitus
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to not modify the current PREA PMRs (b) (4)
 - (b) (4)
However, the Division also note that there are several for T2DM that are being evaluated for use in children (10-17 years of age). It is possible that these studies may demonstrate that PK/PD and efficacy characteristics in adolescent children are similar to adults. If this is proven to be true then formal PK/PD studies may not be needed in the future. Currently these data have not been collected and it is still unknown whether PK/PD/efficacy is similar between children with T2DM and adults with T2DM. Therefore the PeRC agrees that the PREA requirements for this product should not be changed at this time.
 - (b) (4)
 - The PeRC recommend that the Division inform the sponsor that their request to amend their PREA requirement is denied (b) (4)

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/s/

GEORGE E GREELEY
03/04/2014

From: Madara, Patricia
To: ["daniel.coleman@boehringer-ingenheim.com"](mailto:daniel.coleman@boehringer-ingenheim.com)
Cc: heidi.reidies@boehringer-ingenheim.com; kathryn.jason@boehringer-ingenheim.com
Subject: RE: NDA 204629 empagliflozin Label Comments
Date: Friday, January 24, 2014 9:49:00 AM
Attachments: [image001.png](#)
[FDA to BI 204629 empagliflozin fpi draft 2014 01 24.doc](#)
[FDA to BI Jardiance container and carton label revisions_24Jan14.pdf](#)
Importance: High

Dan;

I have attached the revised full prescribing information (track changes). I suggest that you incorporate all revisions except those for which you have questions or require clarification. If you would like to suggest any edits to our revisions, please provide your rationale. I need to request that your comments be returned to us by January 29th.

I have attached the requested revisions to your carton and container labeling. These revisions are recommended after review by the Division of Medication Error Prevention and Analysis. Please incorporate these revisions and resubmit the labeling officially to your NDA.

Finally, the following general revisions should be incorporated throughout the label, if they are applicable.

-
General Revisions

1. If there are any instances of the symbol '<' or '>' in the text, revise to use appropriate wording. The 'greater than' and 'less than' symbols are dangerous abbreviations that could be interpreted opposite of its intended meaning.
2. If there are any trailing zeros, remove them (i.e., 5.0 mg to 5 mg, 1.0 mL to 1 mL). The use of trailing zeros (i.e., 1.0 mL) can lead to 10 fold overdoses if the decimal is not seen.

Please contact me if you have any questions. Please confirm receipt.

Sincerely;
Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: daniel.coleman@boehringer-ingenelheim.com [mailto:daniel.coleman@boehringer-ingenelheim.com]
Sent: Wednesday, January 22, 2014 12:14 AM
To: Madara, Patricia
Cc: heidi.reidies@boehringer-ingenelheim.com; kathryn.jason@boehringer-ingenelheim.com
Subject: NDA 204629 empagliflozin Label Comments

Dear Pat,

We are eagerly waiting for the FDA comments and proposals for the empagliflozin labeling expected by Friday Jan 24.

Would you kindly plan to email the comments to me as soon as they are available even if they are issued as a formal paper correspondence?

Heidi and Kathryn have asked if you could kindly also copy them on any emails regarding empagliflozin so that we can respond as promptly as possible.

If you have time to give us a further update on when we might expect label comments, it would be greatly appreciated.

Thanks and best regards,

Dan



Daniel T. Coleman Ph.D.

Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5081
daniel.coleman@boehringer-ingenelheim.com

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

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/s/

PATRICIA J MADARA
02/27/2014

From: Madara, Patricia
To: ["daniel.coleman@boehringer-ingenheim.com"](mailto:daniel.coleman@boehringer-ingenheim.com)
Cc: heidi.reidies@boehringer-ingenheim.com; kathryn.jason@boehringer-ingenheim.com
Subject: RE: NDA 204629 empagliflozin Label Comments
Date: Saturday, February 01, 2014 10:07:00 AM
Attachments: [image001.png](#)
Importance: High

Hi Dan;

I forwarded your email and request for a tcon to the Division of Medication Error Prevention and Analysis (DMEPA). They have responded with the following comments, recommendations and requests for additional information.

We are happy to discuss our recommendations further. We would like to note that the recommendations quoted in your email are targeted to help prevent selection of the wrong strength of the product and are based on post-marketing experience and DMEPA's Container Labels and Carton Labeling Guidance[1]. More specifically:

- Revise the font color of the proprietary name (b) (4) or revise the color scheme of the 25 mg strength (b) (4) so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

Our practical experience indicates that when the product has several strengths, but shares the color for the proprietary name and one of the strengths, selection errors can occur because the same color is used on different labels, which reduces label differentiation between different strengths. In your specific example, by using the (b) (4) color for the proprietary name, you reduce the difference between the labels because one of your strengths is also expressed in (b) (4). As a result, labels for both of your strengths contain more (b) (4) than any other color which reduces differentiation. Additionally, according to the Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors Guidance, the Sponsors should ensure that the product strength stands out on the container label and carton labeling when there are multiple strengths (p.10). Appropriate techniques for this purpose should be used like boxing, prominent typeface, color differentiation, etc. However, use of (b) (4) color in excess on both labels, reduces differentiation between the strengths.

- Change the (b) (4) block on either 10 mg strength or 25 mg strength, as having (b) (4) color blocks on two strengths decreases the differentiation between the two strengths.

Both labels are mostly white and black with a specific color for a proprietary name and two color blocks (i.e., three little blocks making up a big block) on the upper part of the principal display panel (PDP) and around the strength of the product. Thus, it appears that these color blocks represent the differentiation strategy between the labels. However, both of your labels use (b) (4) color for one of the little blocks on the PDP for both strengths, which by itself decreases the differentiation between the

products. Please refer to aforementioned statements regarding strength differentiation.

Overall though, the use of (b) (4) color on both of your labels decreases the differentiation between the strengths of the product, as a result, selection errors can occur.

As we stated previously, we are more than happy to discuss our recommendations further. However, before we do so, we would like to get some information regarding your new global product design such as:

1. What do you plan to do in terms of the new global design?
2. What changes are you anticipating?
3. Have you done any labeling comprehension studies on your new global design? If so, can you please provide that information to the Agency?

Please send any response officially to your NDA. Please confirm receipt of this email.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: daniel.coleman@boehringer-ingenelheim.com [mailto:daniel.coleman@boehringer-ingenelheim.com]

Sent: Monday, January 27, 2014 8:19 PM

To: Madara, Patricia

Cc: heidi.reidies@boehringer-ingenelheim.com; kathryn.jason@boehringer-ingenelheim.com

Subject: RE: NDA 204629 empagliflozin Label Comments

Dear Pat,

Following our initial internal meetings to discuss the FDA-proposed revisions to the carton and container labeling, we are requesting a short telecon with representatives from the Division of Medication Error Prevention and Analysis to further discuss their requests to:

- Revise the font color of the proprietary name (b) (4) or revise the color scheme of the 25 mg strength (b) (4) so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
- Change the (b) (4) block on either 10 mg strength or 25 mg strength, as having

(b) (4) color blocks on two strengths decreases the differentiation between the two strengths.

These proposed changes are in conflict with Boehringer Ingelheim's new global design for carton and container labeling. The purpose of our meeting is to better understand these FDA comments and to jointly consider possible options to address the concerns while minimizing deviations from the global design. Please note that FDA's input to this NDA will also be considered when preparing future NDA submissions.

We are available at your earliest convenience to discuss.

Please contact me if you have any questions or as soon as you can set up a time for a brief telecon.

Best Regards,

Dan



Daniel T. Coleman Ph.D.

Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5081
daniel.coleman@boehringer-ingelheim.com

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Friday, January 24, 2014 9:50 AM
To: Coleman,Dr.,Daniel (DRA) BIP-US-R
Cc: Reidies,Heidi (DRA) BIP-US-R; Jason,Dr.,Kathryn (DRA) BIP-US-R
Subject: RE: NDA 204629 empagliflozin Label Comments
Importance: High

Dan;

I have attached the revised full prescribing information (track changes). I suggest that you incorporate all revisions except those for which you have questions or require clarification. If you would like to suggest any edits to our revisions, please provide your rationale. I need to request that your comments be returned to us by January 29th.

I have attached the requested revisions to your carton and container labeling. These revisions are recommended after review by the Division of Medication Error Prevention and Analysis. Please incorporate these revisions and resubmit the labeling officially to your NDA.

Finally, the following general revisions should be incorporated throughout the label, if they are applicable.

General Revisions

1. If there are any instances of the symbol '<' or '>' in the text, revise to use appropriate wording. The 'greater than' and 'less than' symbols are dangerous abbreviations that could be interpreted opposite of its intended meaning.
2. If there are any trailing zeros, remove them (i.e., 5.0 mg to 5 mg, 1.0 mL to 1 mL). The use of trailing zeros (i.e., 1.0 mL) can lead to 10 fold overdoses if the decimal is not seen.

Please contact me if you have any questions. Please confirm receipt.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: daniel.coleman@boehringer-ingelheim.com [<mailto:daniel.coleman@boehringer-ingelheim.com>]

Sent: Wednesday, January 22, 2014 12:14 AM

To: Madara, Patricia

Cc: heidi.reidies@boehringer-ingelheim.com; kathryn.jason@boehringer-ingelheim.com

Subject: NDA 204629 empagliflozin Label Comments

Dear Pat,

We are eagerly waiting for the FDA comments and proposals for the empagliflozin labeling expected by Friday Jan 24.

Would you kindly plan to email the comments to me as soon as they are available even if they are issued as a formal paper correspondence?

Heidi and Kathryn have asked if you could kindly also copy them on any emails regarding empagliflozin so that we can respond as promptly as possible.

If you have time to give us a further update on when we might expect label comments, it would be greatly appreciated.

Thanks and best regards,

Dan



Daniel T. Coleman Ph.D.

Regulatory Affairs

Boehringer Ingelheim Pharmaceuticals, Inc.

Ridgefield, Connecticut

P: 203 798 5081

daniel.coleman@boehringer-ingelheim.com

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/s/

PATRICIA J MADARA
02/01/2014

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenheim.com
Subject: IND 102145 and NDA 204629 Request to revise pediatric PK study and update pediatric plan
Date: Monday, November 18, 2013 2:29:00 PM
Importance: High

IND 102145
NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and to your pending New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, both for empagliflozin tablets, 10 mg and 25 mg.

In addition, we reference your draft pediatric PK protocol submitted to IND 102145 on July 19, 2013. We have reviewed the submission and have the following comments and requests:

- **The exclusion criteria in your proposed pediatric PK protocol (1245.87) lists the following for the renal impairment:**
“Impaired renal function defined as estimated Glomerular Filtration Rate [eGFR] < ^(b)₍₄₎ ml/min/1.73m² (Schwartz formula) as determined at screening”
- **This criteria should be changed to eGFR < 90 ml/min/1.73m² to minimize any confounding factors for PKPD data.**
- **Please submit a revised pediatric PK protocol to your IND and update the pediatric plan submitted to your NDA.**

Thanks for your help. **Please confirm receipt of this email.**

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
11/19/2013

**PeRC PREA Subcommittee Meeting Minutes
November 6, 2013**

PeRC Members Attending:

Lynne Yao
Robert Nelson
Hari Cheryl Sachs
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Julia Pinto
William J. Rodriguez
Peter Starke
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Andrew Mosholder
Gregory Reaman
Barbara Buch
Martha Nguyen
Dianne Murphy
Jane Inglese

Guests Attending:

Nichella Simms (PMHS)
Erica Radden (PMHS)
Donna Snyder (PMHS)
Kimberly Compton (DAAAP)
Ellen Fields (DAAAP)
Srikanth Nallani (DAAAP)
Sofia Chaudhry (DPARP)
Susan Limb (DRPAR)
Satjit Brar (OCP)
Sandy Chang (DPP)
Glenn Mannheim (DPP)
Jing Ahang (DPP)
Lawren Slate (OCP)
Carla Epps (DGIEP)
David Joseph (DGIEP)
Rigo Roca (DAAAP)
William Chong (DMEP)
Todd Bourcier (DMEP)
Josh Lloyd (DAAAP)
Mukesh Summan (DMEP)

Swati Patwardhan (DAAAP)
Brittany Goldberg (DAVP)
Katherine Schumann (DAVP)
Yodit Belew (DAVP)
Karen M. Mahoney (DMEP)
Manoj Khurana (OCP)
Lokesh Jain (OCP)

Agenda

11:00	NDA	204629	Jardiance (empagliflozin) Partial Waiver/Deferral/Plan
11:15	NDA		(b) (4)
11:30	NDA		
11:45	NDA		
	NDA		
	NDA		

Jardiance (empagliflozin) Partial Waiver/Deferral/Plan

- NDA 204629 seeks marketing approval for Jardiance (empagliflozin) for the treatment of Type 2 diabetes mellitus.
- The application was submitted on March 5, 2013, and has a PDUFA goal date of March 5, 2014.
- The application triggers PREA as directed to a new active ingredient.
- A waiver is being requested for pediatric patients aged birth to less than 10 years because studies would be impossible or highly impractical.
- *Division justification for waiver:* The prevalence of type 2 diabetes mellitus in pediatric patients less than 10 years of age is very low, which makes studies in this age range very difficult, if not impossible. Waiver of this age range is consistent with what has been done for other agents for the treatment of type 2 diabetes mellitus.
- A deferral is being requested for pediatric patients aged 10 to less than 18 years because adult studies are completed and the product is ready for approval.
- The sponsor proposes to conduct the following studies:
 - Study 1: PK/PD study in pediatric patients with type 2 diabetes mellitus
 - Protocol Submission: July 31, 2013
 - Study Completion: December 31, 2014
 - Study Report Submission: June 30, 2015
 - Study 2: Safety and efficacy study in pediatric patients with type 2 diabetes mellitus
 - Protocol Submission: September 30, 2014
 - Study Completion: August 31, 2018
 - Study Report Submission: April 30, 2019
- In the Division's view, a more detailed description of the proposed phase 3 trial is not possible at this time. The trial design and sample size estimates are dependent on how many doses are selected for the study, which will be based on the pending PK/PD study.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to less than 10 years because studies are impossible or highly impractical. This age cut off for a waiver has been accepted for all products to treat T2DM to date.

- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 10 to less than 18 years because the product is ready for approval in adults. The PeRC agreed to the proposed timelines for the deferred studies. Clinical efficacy studies are being delayed until non-clinical information related to a renal and bone safety signal can be reviewed.

(b) (4)

3 Page(s) have been Withheld in Full as b4
(CCI/TS) immediately following this page

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/s/

JANE E INGLESE
11/18/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenheim.com
Subject: NDA 204629 Request for Information
Date: Wednesday, October 30, 2013 2:09:00 PM
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review your application and have the following comment and request for information:

- **We are unable to locate the narrative for patient 1245.0025. (b) (4) who died in the empagliflozin development program. Please provide us with a narrative for this death, or direct us to where this information can be found.**

Submit your responses officially to NDA 204629. Contact me if you have any questions.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/30/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenelheim.com
Subject: RE: NDA 204629 (empagliflozin) Request for Information #2 (28Oct13)
Date: Monday, October 28, 2013 12:59:00 PM
Importance: High

Dan,

Regarding the information request below, we would appreciate a response by Wednesday, October 30th. Please let me know if this is not possible and provide an alternative timeframe for submission.

Sincerely;

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Madara, Patricia
Sent: Monday, October 28, 2013 12:57 PM
To: daniel.coleman@boehringer-ingenelheim.com
Subject: NDA 204629 (empagliflozin) Request for Information #2 (28Oct13)
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review your application and have the following comment and request for information:

- **We are unable to reproduce the population pharmacokinetic analysis using the submitted control stream files for base model (2018.ctf) and final model (2019.ctf) files and using the data (tranpk.csv submitted as tranpk.xpt) file. Please check if the data-sets and model files submitted**

to the Agency are accurate and accordingly submit the revised files and any additional information that could help resolve this. We are using NONMEM v7.2 with gfortran compiler. The NONMEM run terminates with the error message "0PROGRAM TERMINATED BY OBJ ERROR IN CELS WITH INDIVIDUAL 1 ID= 1.20100000000000E+03 SUM OF "SQUARED" WEIGHTED INDIVIDUAL RESIDUALS IS INFINITE MESSAGE ISSUED FROM ESTIMATION STEP AT INITIAL OBJ. FUNCTION EVALUATION". Comparing the "lst" files with our run to that submitted by you, it only differs in terms of number of data records. [FDA re-run of the model: "NO. OF DATA RECS IN DATA SET: 41001, TOT. NO. OF OBS RECS: 12502, TOT. NO. OF INDIVIDUALS: 2761 versus the Sponsor's Analysis: NO. OF DATA RECS IN DATA SET: 43763, TOT. NO. OF OBS RECS: 12503, TOT. NO. OF INDIVIDUALS: 2761].

Submit your responses officially to NDA 204629. Contact me if you have any questions.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/28/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenheim.com
Subject: NDA 204629 - REQUEST FOR INFORMATION
Date: Monday, October 28, 2013 12:37:00 PM
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review your application and have the following request for information:

- **For all cases sent to your hepatic events adjudication committee, please submit to us the adjudication packages, and the adjudication reports completed by the hepatic experts.**

You may submit this information informally, via email but also submit your responses officially to NDA 204629. Contact me if you have any questions.

-
Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/28/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingelheim.com
Subject: NDA 204629 (empagliflozin) Request for Information.
Date: Thursday, October 10, 2013 2:53:00 PM
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review your application and have the following requests for information:

- 1. Please provide any data you may have on the effect of SGLT2 inhibitors on assays that assess glycemic control using 1,5-anhydroglucitol.**
- 2. Please indicate whether you have any studies ongoing or planned to study this possible effect.**
- 3. Please indicate whether your current understanding of this effect would support labeling, and if so, please propose labeling language.**

You may submit this information informally, via email but also submit your responses officially to NDA 204629. Contact me if you have any questions.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/10/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenelheim.com
Subject: NDA 204629: Request for Information
Date: Tuesday, October 08, 2013 11:11:00 AM
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review your application and have the following urgent requests for information:

1. **The protocol for your dedicated cardiovascular outcomes trial (trial 1245.25) states that the** (b) (4)

[REDACTED]

. Please provide detailed description of any firewall procedures that were implemented.

We request your response by October 15, 2013.

2. **We attempted to pre-announce an inspection of Dr. Joseph Rivas (Site #10109). It was difficult to track down Dr. Rivas as he did not answer the phone at the listed site. Dr. Rivas does not have any of the medical records from Study 1245.23. He indicated that all records were stored at** (b) (4) **but he has no contact information for this company.**

Please let us know where the medical records for Dr. Rivas's site during Study 1245.23 are stored and provide correct contact information so that we can arrange an inspection. We require this information as soon as possible.

3. **Your clinical study reports for 1245.23 and 1245.31 mention "001-MCS-80-609 Corporate Standard Operating Procedure: Serious Non-Compliance and Suspected Fraud in Medicine & QRPE. Version 4.0," which deals with the corrective actions taken as a result of fraud at Dr. Ahmed's site 10001. Please submit this standard operating procedure (SOP).**

You may submit this information informally, via email but also submit your responses officially to NDA 204629. Contact me if you have any questions.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
10/08/2013

Executive CAC

Date of Meeting: October 1st, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Aisar Atrakchi, Ph.D., DPP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Team Leader
Mukesh Summan, PhD, DABT, DMEP, Presenting Reviewer

Author of Draft: Dr.'s Mukesh Summan and Todd Bourcier

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 204629
Drug Name: Empagliflozin
Sponsor: Boehringer Ingelheim Pharmaceuticals Inc

Background:

Empagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor. The sponsor is seeking an indication for the treatment of type 2 diabetes mellitus (T2DM).

Mouse Carcinogenicity Study

Carcinogenic assessment in CD-1 mice was initiated at doses of 100, 300 and 1000 mg/kg for both male and female mice, with dual control groups (0.5% hydroxyethyl cellulose in water). This was in accordance with the Committee's dosing recommendations. Decreased survival in the 1000 mg/kg males resulted in early termination for this group at week 97. As all high dose males and females were terminated at weeks 97 and 102, respectively, the high dose is considered adequate for tumor assessment and statistical evaluation. The survival rate across the remaining treatment groups was similar to the vehicle control groups. Drug exposure at the 100, 300 and 1000 mg/kg dose groups provided multiples of 4x, 11x, and 45x MRHD in males, and multiples of 7x, 28x, and 62x MRHD in females, relative to the clinical dose of 25 mg.

Results

Renal adenoma or carcinoma (combined) increased primarily in the 1000 mg/kg males and is clearly related to empagliflozin treatment when combined (see table below). The single adenoma in the 300 mg/kg male was not significant by pair-wise testing and is within an older historical control range for this tumor type. The renal neoplasms occurred in the presence of tubular injury in the dosed groups, and is consistent with the results of several other SGLT2 inhibitors.

Summary of Mouse Tumor Statistics

Summary of tumors with any significant difference from controls †									
Tissue/ Tumor	Sex	Empagliflozin (mg/kg/day)					Statistics (p-value) ^a		
		0	0	100	300	1000	Trend	Pair-wise Mid-dose	Pair-wise High-dose
Kidney: adenoma, tubular	M	0	0	0	1	3	0.002	nss	0.028
Kidney: malignant carcinoma, tubular	M	0	0	0	0	2	nss	NA	nss
Kidney: adenoma & carcinoma combined	M	0	0	0	1	5	<0.0001	nss	0.002

† Statistical analyses summarized from FDA statistics review (Dr. Min)

F = female, M = male, nss = not statistically significant, NA = not applicable

^a Statistical analysis with controls combined.

Rat Carcinogenicity Study

Carcinogenic assessment in Wistar (Han) rats was initiated at doses of 100, 300, and 700 mg/kg, with dual control groups (0.5% hydroxyethyl cellulose in water), and in accordance with the Committee's dosing recommendations. The survival rate across the treatment groups was similar to the vehicle control groups. Drug exposure at the 100, 300, and 700 mg/kg dose groups provided multiples of 17x, 26x, and 42x MRHD in males and 21x, 45x, and 72x MRHD in females relative to the clinical dose of 25 mg.

Results

The incidence of hemangioma increased in male rats with a dose-dependence that was statistically significant by trend and pair-wise testing (to HD), relative to the combined control groups (see table below). The increase was nearly entirely due to a higher incidence of hemangioma in the mesenteric lymph nodes. The lymph nodes showed signs of increased activity at all doses in males and, to a lesser extent, in females. This was characterized by increased trafficking of sinus histiocytes, mast cells, sinus erythrocytes and pigmented macrophages. The cause of the lymphadenitis is uncertain, but is plausibly related to the increased intestinal dilatation and glandular stomach discoloration observed in these dose groups.

Summary of Rat Tumor Statistics

Summary of tumors with any significant difference from controls †									
Tissue/ Tumor	Sex	Empagliflozin (mg/kg/day)					Statistics (p-value) ^a		
		0	0	100	300	700	Trend	Pair-wise Mid-dose	Pair-wise High-dose
Whole body/cavity : heman- gioma	M	3	0	2	5	9	0.001	nss	0.002
Testis: Leydig cell tumor	M	2	0	4	7	6	nss	0.008	nss

† Statistical analyses summarized from FDA statistics review (Dr. Min)

F = female, M = male, nss = not statistically significant, NA = not applicable

^a Statistical analysis with controls combined.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee considered the study to be adequate, noting prior Exec CAC protocol agreement.
- The Committee concurred that the increased incidence of renal tubular adenoma or carcinoma (combined) in males was drug related. No drug-related neoplasms were reported in females.

Rats:

- The Committee considered the study to be adequate, noting prior Exec CAC protocol agreement.
- The Committee concurred that the increase in the incidence of whole body/cavity hemangiomas in the high dose males was clearly drug related.
- The Committee noted that although the numerical increased incidences of testicular Leydig cell tumors did not reach statistical significance by current statistical criteria for a common tumor type, Leydig cell tumors have been observed in 3 of 5 other SGLT2 inhibitor carcinogenicity studies, and thus are potentially drug related. No drug-related neoplasms were reported in female rats.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

- /Division File, DMEP
- /Todd Bourcier, PhD/Team Leader, DMEP
- /Mukesh Summan, PhD, DABT/Reviewer, DMEP
- /Patricia Madara/PM, DMEP
- /ASeifried, OND IO

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/s/

ADELE S SEIFRIED
10/03/2013

DAVID JACOBSON KRAM
10/03/2013



NDA 204629

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jardiance (empagliflozin) tablets, 10 mg and 25 mg.

We are reviewing the chemistry, manufacturing and controls (CMC) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1 Provide the rationale for choosing film-coated tablets in the final formulation of the drug product rather than (b) (4) tablets as manufactured using Trial Formulations I and II.
- 2 The acceptance criteria for Particle Size distribution should include acceptable particle size distribution in terms of the percent of total particles in given size ranges, for example, D10, D50, and D90. Incorporate appropriate acceptance criteria for a 3-point particle size distribution as part of the Drug Substance Specifications. See ICH Q6A “*Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*” for guidance.
(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm>).
- 3 Provide a description of the analytical procedure for Identification by UV used in the drug product specifications.
- 4 The proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes is not supported by data. We recommend that you revise and implement the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 minutes and provide an updated specifications table for the drug product.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Branch Chief (Acting)
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

DANAE D CHRISTODOULOU
09/16/2013



NDA 204629

MID-CYCLE COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jardiance (empagliflozin) tablets, 10 mg and 25 mg.

We also refer to the teleconference between representatives of your firm and the FDA on September 5, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 5, 2013; 3:00 PM eastern time
Application Number: NDA 204629
Product Name: Jardiance (empagliflozin) 10 mg and 25 mg tablets
Indication: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc
Meeting Chair: Karen M. Mahoney, M.D.
Meeting Recorder: Patricia Madara

FDA Attendees

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director (Acting)
Karen M. Mahoney, M.D.	Diabetes Team Leader
William Chong, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
Mukesh Summan, Ph.D.	Pharmacology/Toxicology Reviewer
Patricia Madara, M.S.	Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Lokesh Jain, Ph.D.	Clinical Pharmacology Team Leader
Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer

Office of Clinical Pharmacology; Division of Pharmacometrics

Nitin Mehrotra, Ph.D.	Team Leader (Acting)
-----------------------	----------------------

Office of Program & Strategic Analysis; Program Evaluation and Implementation Staff

Kimberly Taylor	Operations Research Analyst
-----------------	-----------------------------

Boehringer Ingelheim Pharmaceuticals, Inc. Attendees

Uli Broedl, M.D.	Assoc. Head, Therapeutic Area Metabolism
Daniel Coleman, Ph.D.	Sr. Assoc. Director, Regulatory Affairs
Stefan Hantel, Ph.D.	Project Biostatistician, Medical Data Services
Sabine Jeck-Thole, M.D.	Head Risk Management TA Metabolism and Virology

Sabine Luik, M.D. MBA.	Sr. VP, Medicine & Regulatory Affairs
Sreeraj Macha, Ph.D.	Team Member, Clinical PK & PD
Roman Messerschmid, Ph.D	R&D Project Leader, BI
Joanne Palmisano, M.D. FACP	Vice President, Regulatory Affairs
Heidi Reidies	Executive Director, Regulatory Affairs
Afshin Salsali, M.D.	Clinical Project Leader, Medicine
Beth Weinberg, R.Ph.	Advisor, Regulatory Affairs, Eli Lilly
Marion Wienrich, Prof., Ph.D.	International Project Leader, BI
Markus Wolters, Ph.D.	International Project Management, BI
Dalu Xu, Ph.D.	Project Medical Writer, Clinical Research Germany

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES (Preliminary)

A. Clinical

- i. We have found the following imbalances that do not favor empagliflozin:
 - a) elevated transaminases and multiple Hy's Law cases
 - b) lung cancer and melanoma
- ii. The best dose for approval (10 mg vs. 25 mg) remains unclear. Efficacy of the 10 mg dose is not different from the 25 mg dose and there may be an increased number of adverse events with the 25 mg strength.

B. Pharmacology / Toxicology

- i. The draft label proposes pregnancy category (b) (4) [REDACTED] (b) (4) [REDACTED]. To adequately communicate this risk, empagliflozin will therefore be Pregnancy Category C with a description of the risk, similar to the label for canagliflozin.

C. Clinical Pharmacology

- i. The dose-response data from Phase 2 trials (1245.09 and 1245.10) and Phase 3 trials (1245.20, .19, and .23) shows modest to no benefit of the 25 mg over the 10 mg dose with regards to HbA1c reduction from baseline. The exposure-response data and population PKPD report also suggest that both doses provide near maximal response. Therefore, we are of the opinion that 10 mg QD could be the optimal dose for Empagliflozin.
- ii. Dose-response data from the dedicated trial in renal impairment shows that empagliflozin does not appear to be effective in patients with baseline eGFR 30-45 mL/min/1.73m² (i.e. Moderate Renal Impairment B), and certainly ineffective in severe renal impairment (eGFR < 30 mL/min/1.73m²). .
- iii. Although the 25 mg strength shows a reduction in HbA1c from baseline in patients with mild renal impairment, the 10 mg dose was not evaluated in this trial. Therefore, predictive capability of the population PK/PD model is critical to inform the HbA1c response of 10 mg Empagliflozin in patients with renal impairment. We are reviewing the dose-response data and robustness of the population PKPD model to evaluate if the population PKPD model can be used to reliably predict the response following 10 mg dose. To facilitate further review of this, we request that you provide some additional information regarding the population PKPD model.

3.0 INFORMATION REQUESTS

- A. You will be receiving information requests from the following disciplines:
 - i. Chemistry / Manufacturing /Controls
 - ii. Biopharmaceutics
 - iii. Clinical Pharmacology (see above)

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

You did not submit a REMS with your application and at this time, the Office of Surveillance and Epidemiology is not proposing a REMS for empagliflozin. However, they may recommend enhanced pharmacovigilance.

5.0 ADVISORY COMMITTEE MEETING

At this time, the advisory committee meeting for empagliflozin is scheduled for December 13, 2013.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late-cycle meeting will be held no later than approximately 12 days prior to the advisory committee meeting. A briefing document will be provided no later than eight days before the late-cycle meeting.

7.0 APPLICANT QUESTIONS / DISCUSSION

Boehringer Ingelheim (BI) asked how the blinding in the ongoing cardiovascular outcomes trial (CVOT) would be maintained. FDA indicated that this issue would be discussed at a separate meeting with the firewalled team.

The clinical pharmacology group at BI asked for clarification regarding the exposure – response analysis. FDA responded that data for the dose-response and the robustness of the population PK/PD model were being reviewed. In particular, the model is being assessed to determine whether it can be relied upon to predict HbA1c response for the 10 mg dose in Moderate Renal Impairment. It was noted that FDA would be issuing a detailed information request, asking for additional analyses to facilitate review of this topic.

BI asked about the possibility of submitting additional safety information related to the safety concerns that were raised (i.e., increased transaminases, Hy's law cases, lung cancer and melanomas). The applicant indicated data from three additional studies – two studies not included in the NDA and data from a controlled extension for a submitted study. BI noted they would provide additional details in an email. FDA commented that the data could be submitted but provided no guarantee that FDA would be reviewed. FDA also commented that under 'The Program' submission of unsolicited data by the applicant could trigger an extension of the review cycle.

The meeting ended.

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/s/

JEAN-MARC P GUETTIER
09/13/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenelheim.com
Subject: NDA 204629 (empagliflozin) Request for Information
Date: Sunday, September 08, 2013 9:46:00 PM
Attachments: [Info Request_NDA_204629.pdf](#)
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

As mentioned at the recent midcycle communication, I have attached an information request from the clinical pharmacology review team. You may receive this request in an "information request" letter also.

Submit your response officially to NDA 204629. Contact me if you have any questions.

Please confirm receipt of this email.

Sincerely;

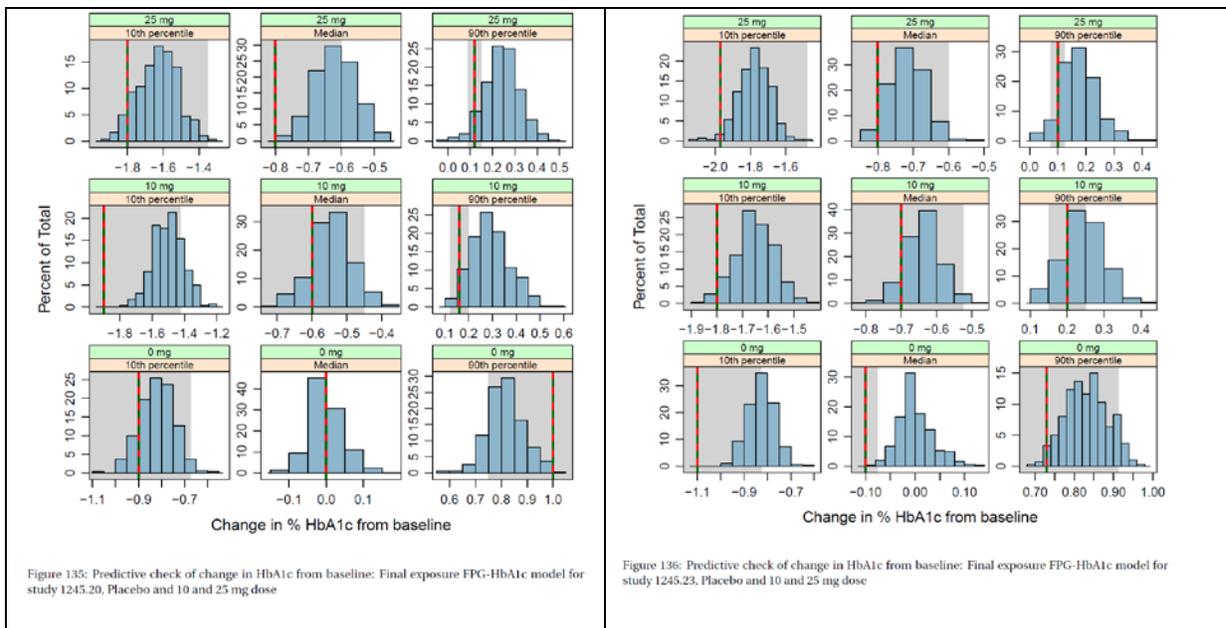
Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Information Request:

Based on our review of the dose-response and population PKPD report (U12-2525-01), we need you to address the following information request to facilitate further review of your submission:

- a. We note that with regards to the visual predictive checks (VPCs), there appears to be a systematic bias in the model predictions e.g. Figures 46, 48, and 50, Pages 148, 150, and 152, respectively the model simulated trough concentrations are underpredicted for the 10% percentile and over predicted for the 90th percentile while capturing the median. This indicates that PK model is not able to capture the inter-individual variability.
- b. Similarly, from VPCs for HbA1c change from baseline, numbers of graphs indicate issues with the predictability, e.g. as shown below.



- c. Specifically, with regards to the VPC figures of Change in HbA1c by Renal Function subgroups, please clarify the following:
 - i. As we understand from the design, the 10 mg dose was not evaluated in Moderate Renal Impairment subjects (eGFR 30 to 60) in Trial 1245.36. However, you show the observed median in the graph for comparison. How many subjects from Moderate RI were there in your analysis and what was the eGFR range. Also, provide number of Moderate RI subjects and eGFR ranges by trial (for 1245.19, .20, .23, and .33) in the analysis data sets used for generating observed data for Figures 154 and 155.
 - ii. Could you explain why the response on average from 25 mg (observed and predicted) is lower than that for 10 mg dose in Moderate RI putting side by side figures 157 and 159, and figures 154 and 155, respectively?

Figure 157, Page 259

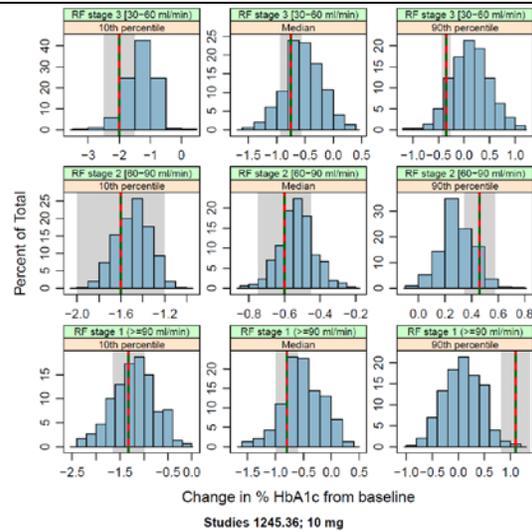


Figure 158, Page 260

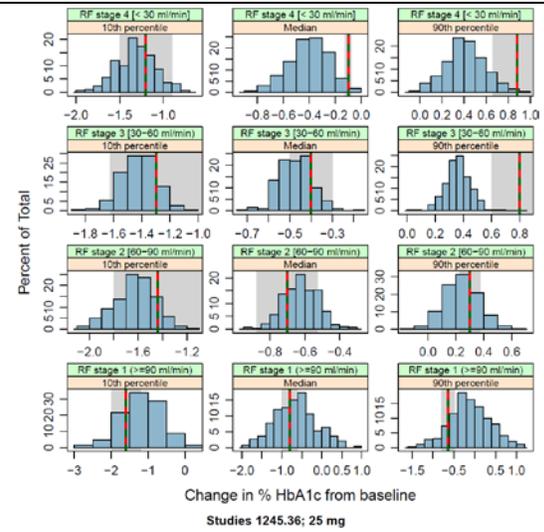


Figure 154, Page 256

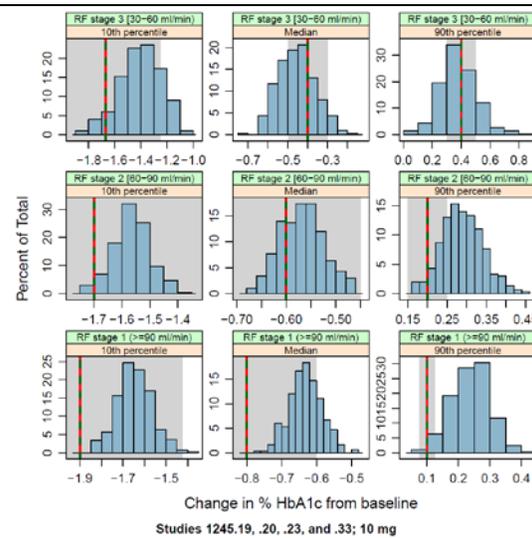
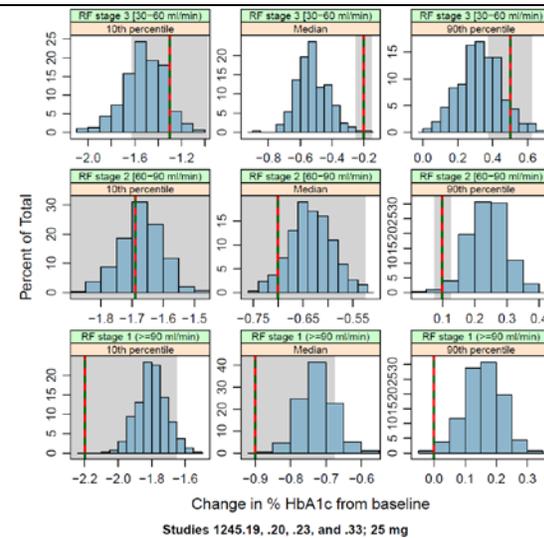


Figure 155, Page 257



d. For Figure 113 on Page 215 of the document, which presents the Observed and simulated HbA1c change from baseline for three trials (1245.19, .20, and .23), please provide similar graphs for individual trials.

- e. From this final population-PKPD model, please provide the point estimate (95%CI) for predicted HbA1c change from baseline for both 10 and 25 mg doses at Week 24 in the following scenarios:
- i. For Trial 1245.19 data
 - ii. For Trial 1245.20 data
 - iii. For Trial 1245.23 data
 - iv. For Trial 1245.33 data
 - v. Moderate Renal Impairment A (eGFR 30 to 45) for Trial 1245.36
 - vi. Moderate Renal Impairment B (eGFR 45 to 60) for Trial 1245.36
 - vii. Moderate Renal Impairment (eGFR 30 to 60) for Trial 1245.36
 - viii. Mild Renal Impairment (eGFR 60 to 90) for Trial 1245.36

(Observed median eGFR for each subgroup in Trial 1254.36 could be used for prediction purpose)

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/s/

PATRICIA J MADARA
09/20/2013

From: Madara, Patricia
To: ["daniel.coleman@boehringer-ingelheim.com"](mailto:daniel.coleman@boehringer-ingelheim.com)
Cc: heidi.reidies@boehringer-ingelheim.com
Subject: RE: NDA 204629 empagliflozin - request for information
Date: Tuesday, August 27, 2013 4:20:00 PM
Attachments: [image001.png](#)

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

In addition, reference our email request for information sent on August 21, 2013 and your response on August 23, 2013, by email. We have reviewed your proposals and have the following comments.

1. The proposed listing with links to the available narratives is acceptable.
2. Provide adjudicated case summary documentation for all other events for which narratives are not available, rather than on a "per patient" basis.

Please submit the information officially to your NDA. Thanks for your help!

Please confirm receipt of this email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

From: daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]
Sent: Friday, August 23, 2013 2:41 PM
To: Madara, Patricia
Cc: heidi.reidies@boehringer-ingelheim.com
Subject: RE: NDA 204629 empagliflozin - request for information

Dear Pat,

To respond to this request, BI is proposing to provide **for all 4-point MACE events captured in the cardiovascular safety meta-analysis** report (the primary endpoint):

- Listing of patients with such events, with hyperlinks to narratives in the NDA if

available (see below)

- Adjudicated case summary documentation on a “per patient” basis. An example of case summary documentation is provided with this email, for convenient reference.

Consistent with Section 10.5 of the preNDA meeting information package submitted 10/26/12 and agreed by the FDA in the minutes of this meeting (12/17/12, question 5), BI did not prepare narratives for cardiovascular outcome events from the ongoing cardiovascular safety study (1245.25). Please note that [REDACTED] (b) (4) adjudicated 4-point MACE events in the meta-analysis report are from Study 1245.25. BI proposes to prepare individual narratives on request, if needed.

Please confirm that this is acceptable.

Best Regards,

Dan



Daniel T. Coleman Ph.D.

Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5081
daniel.coleman@boehringer-ingelheim.com

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Wednesday, August 21, 2013 4:37 PM
To: Reidies, Heidi (DRA) BIP-US-R; Coleman, Dr., Daniel (DRA) BIP-US-R
Subject: NDA 204629 empagliflozin - request for information
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Heidi and Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review the application and have the following request for additional information:

- **We are unable to locate narratives for the CEC adjudicated events. If these have been submitted, please direct us to where they can be found. If they have not been submitted, please submit these narratives for our review as soon as possible.**

You may submit this information by email but also submit it officially to your NDA. Thanks for your help!

Please confirm receipt of this email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
08/27/2013

From: Madara, Patricia
To: heidi.reidies@boehringer-ingenheim.com; daniel.coleman@boehringer-ingenheim.com
Subject: NDA 204629 empagliflozin - request for information
Date: Wednesday, August 21, 2013 4:35:00 PM
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Heidi and Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review the application and have the following request for additional information:

- **We are unable to locate narratives for the CEC adjudicated events. If these have been submitted, please direct us to where they can be found. If they have not been submitted, please submit these narratives for our review as soon as possible.**

You may submit this information by email but also submit it officially to your NDA. Thanks for your help!

Please confirm receipt of this email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
08/21/2013

From: Madara, Patricia
To: ["daniel.coleman@boehringer-ingelheim.com"](mailto:daniel.coleman@boehringer-ingelheim.com)
Subject: RE: NDA 204629 (empagliflozin)
Date: Tuesday, July 30, 2013 10:24:00 PM
Attachments: [image001.png](#)
Importance: High

Hi Dan;

Thank you for this information. To help collect the data required, we have the following recommendations:

1. Often the critical information can only be obtained at the site of the occurrence from the investigator, and is NOT available in the standardized case report forms.
2. The information in the narratives should not just be "data-dumps" of case report information.
3. The difficult problem is one of medical differential diagnosis of causality, and not just serum chemistries. Reports should be prepared by a physician skilled in clinical differential diagnosis, and not by a project manager, statistician, or other non-medical person.

I hope this is helpful. Please contact me if you have any questions.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]

Sent: Tuesday, July 30, 2013 5:29 PM

To: Madara, Patricia

Subject: RE: NDA 204629 (empagliflozin)

Dear Pat,

We plan to submit the liver dataset (including narratives) to the NDA by Monday August 12.

Please note that, in the interest of time, we are focusing on the narratives for patients treated with empagliflozin.

Best Regards,
Dan



Daniel T. Coleman Ph.D.
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5081
daniel.coleman@boehringer-ingelheim.com

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Monday, July 29, 2013 4:42 PM
To: Coleman,Dr.,Daniel (DRA) BIP-US-R
Subject: RE: NDA 204629 (empagliflozin)

Many thanks. Greatly appreciated.

From: daniel.coleman@boehringer-ingelheim.com [<mailto:daniel.coleman@boehringer-ingelheim.com>]
Sent: Monday, July 29, 2013 4:40 PM
To: Madara, Patricia
Subject: RE: NDA 204629 (empagliflozin)

Hi Pat,

Yes I got it.

I will be discussing with the team tomorrow morning and will be asking for a date.

Best Regards,
Dan



Daniel T. Coleman Ph.D.
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5081
daniel.coleman@boehringer-ingelheim.com

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Monday, July 29, 2013 4:37 PM
To: Coleman,Dr.,Daniel (DRA) BIP-US-R
Subject: RE: NDA 204629 (empagliflozin)

Hi Dan;

Did you get this email? Any timeframe for receipt. Thanks. Pat

From: Madara, Patricia
Sent: Saturday, July 27, 2013 9:32 AM
To: daniel.coleman@boehringer-ingelheim.com
Cc: Madara, Patricia

Subject: RE: NDA 204629 (empagliflozin)
Importance: High

Hi Dan;

Because of overlapping leave schedules, we really need a timeframe for submission of these liver datasets. Please provide a date or estimated date of arrival. As much as possible can also be sent informally via email. Also let me know when to expect the disc.

Sincerely;
Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Madara, Patricia
Sent: Friday, July 12, 2013 12:38 PM
To: 'daniel.coleman@boehringer-ingenelheim.com'
Subject: RE: NDA 204629 (empagliflozin)
Importance: High

NDA 204629

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

In addition, reference our information request sent on June 12, 2013 and your related questions below. We have reviewed your proposals and find them acceptable.

Please send the desk copy disc directly to me at the address below:

*Patricia Madara
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3360
10903 New Hampshire Avenue
Silver Spring, Maryland*

*Use zip code **20903** if shipping via United States Postal Service (USPS).
Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Please confirm receipt of this email.

Sincerely;

Patricia Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Phone: 301-796-1249

From: daniel.coleman@boehringer-ingenelheim.com [mailto:daniel.coleman@boehringer-ingenelheim.com]

Sent: Thursday, July 11, 2013 11:06 AM

To: Madara, Patricia

Subject: RE: NDA 204629 (empagliflozin)

Dear Pat,

Regarding the dataset you requested for evaluation of liver events with the eDISH tool (in your email below and attached);

Please let me know if you have any concerns about the following proposed revisions to the variable names that were requested to be used in the datasets:

1) Standardvariable length

1a) As there is a limit of 8 characters for variable names in the XPT-files that will be provided in the eCTD submission, we will shorten some of the Standardvariable names, e.g.

ALT_REF_HIGH will be changed to ALT_RFH,

BILI_REF_HIGH will be changed to BILI_RFH, and so on.

1b) The files on the additional requested CD/DVD desk copy will be in CPT file format which can have longer variable names. In these CPT files we will use the Standardvariable names requested by the FDA instead of the shortened variable names (above) used in the XPT files. Please note that because of this the Desk copy

will contain different Standardvariable names from the Standardvariable names used in the eCTD version.

2) For some patients there is more than one measurement per date in the liver test data.

2a) Because sometimes multiple samples were taken on a single day we will include an additional variable for the "Time of Exam"
Standardvariable = EXTM, Variablemeans = Time of Exam, Variabletype = Char (HH:MM:SS)

2b) In addition when more than one kit was sent for the same date and time there is more than one measurement reported for the same time on a particular date. To distinguish between these two samples we will include an additional variable for the "Visit Number"
Standardvariable = VISITNUM, Variablemeans = Visit Number, Variabletype = Num

Thanks for your consideration.

Best Regards,

Dan



Daniel T. Coleman Ph.D.

Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5081
daniel.coleman@boehringer-ingelheim.com

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]

Sent: Wednesday, June 12, 2013 5:18 PM

To: Coleman,Dr.,Daniel (DRA) BIP-US-R

Subject: NDA 204629 (empagliflozin)

Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review the data submitted. Please see the attached PDF document containing a request for additional information. Please submit your response officially to the NDA.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
08/01/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingenheim.com
Subject: NDA 204629 (empagliflozin) - REQUEST FOR INFORMATION
Date: Monday, July 29, 2013 4:19:00 PM
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review the application and have additional requests for information related to the SAE cases of lung cancer and melanoma. These cases are listed in Table 2.1.5: 3 “Patients treated for >6 months and reported with melanoma after 6 months” and Table 2.1.5.8: 4, “Patients treated for > 6 months and reported with lung cancer after 6 months” on p. 158 of the Summary of Clinical Safety. Specifically, can you please submit the following information for the cases:

1. Risk factors for lung cancer:

- a) Smoking cigarettes or secondhand exposure**
 - i. duration and quantity of cigarette use (i.e., pack years)**
 - ii. if former smoker, time since last exposure**
- b) Prior history of lung cancer or other cancers**
- c) Family history of lung cancer**
- d) Occupational exposure (asbestos or radon gas)**
- e) Prior history of chest radiation**

2. Risk factors for melanoma:

- a) Family history of melanoma**
- b) Sun exposure: sunburns at childhood and use of tanning beds**
- c) History of basal cell carcinoma or squamous cell carcinoma**
- d) Prior history of melanoma**
- e) Exposure to immunosuppressive agents or history of immunosuppression (i.e., organ transplant history or HIV)**

3. Include the pathology reports (with molecular results if performed), extent and result of the staging evaluations, and treatments administered for the malignancies as well as outcomes.

You may submit this information by email but also submit it officially to your NDA. Thanks for your help!

Please confirm receipt of this email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
07/29/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 204629

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director, Regulatory Affairs

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated and received March 5, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Empagliflozin Tablets, 10 mg and 25 mg.

We also refer to your April 25, 2013, correspondence, received April 26, 2013, requesting review of your proposed proprietary name, Jardiance. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Jardiance, 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 March 5, 2013, 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 Patricia Madara, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
07/25/2013

From: Madara, Patricia
To: daniel.coleman@boehringer-ingelheim.com
Subject: NDA 204629 - 23July13 - Request for information #2 (clinical)
Date: Tuesday, July 23, 2013 4:56:00 PM
Attachments: [23July13_Clinical_Review_Information_Request.pdf](#)
Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review the application and have additional requests for information. Please see the attached PDF document.

You may submit this information by email but also submit it officially to your NDA. Thanks for your help!

Please confirm receipt of this email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

To facilitate our review of NDA 204629 (Empagliflozin), please provide us with the information requested below.

1. Provide a table with information similar to table 5.1.1: 1 in the Summary of Clinical Safety for fatal/non-fatal stroke by age, gender, race, ethnicity, and baseline renal function. A sample table template follows below.

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
	N	%	Per 1000	N	%	Per 1000	N	%	Per 1000	N	%	Per 1000	N	%	Per 1000
By Age (years)															
< 50															
- total															
- w/ event															
≥ 50, < 65															
- total															
- w/ event															
≥ 65, < 75															
- total															
- w/ event															
≥ 75															
- total															
- w/ event															
By Gender															
Male															
- total															
- w/ event															
Female															
- total															
- w/ event															
By Race															
White															
- total															
- w/ event															
Black															
- total															
- w/ event															
Asian															
- total															
- w/ event															
By Ethnicity															
Hispanic															
- total															
- w/ event															
Non-Hispanic															
- total															
- w/ event															
By baseline renal function (eGFR by MDRD)															
> 90															
- total															
- w/ event															
60 to < 90															
- total															
- w/ event															
30 to < 60															
- total															
- w/ event															
< 30															
- total															
- w/ event															
Empa 10 = subjects randomized to Empagliflozin 10 mg at time of event															

Empa 25 = subjects randomized to Empagliflozin 25 mg at time of event
 All Empa = subjects on any randomized dose of Empagliflozin at time of event
 All Comp = all comparators (placebo, metformin, sitagliptin, glimepiride)
 N = total number of subjects
 % = percent of subjects at risk with event
 Per 1000 = incidence per 1000 patient-years at risk

- Provide a table with information on adverse events 30 days, 60 days, 120 days, and 180 days for all treatment emergent adverse events and separately for adverse events of special interest, 4-point MACE, and fatal/non-fatal stroke. A sample table template follows below.

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
30 days from initiation of randomized therapy										
System Organ Class										
- Preferred Term										
Adverse events of special interest										
4-point MACE										
Fatal/Non-fatal stroke										
60 days from initiation of randomized therapy										
System Organ Class										
- Preferred Term										
Adverse events of special interest										
4-point MACE										
Fatal/Non-fatal stroke										
120 days from initiation of randomized therapy										
System Organ Class										
- Preferred Term										
Adverse events of special interest										
4-point MACE										
Fatal/Non-fatal stroke										
180 days from initiation of randomized therapy										
System Organ Class										
- Preferred Term										
Adverse events of special interest										
4-point MACE										
Fatal/Non-fatal stroke										
Empa 10 = subjects randomized to Empagliflozin 10 mg at time of event Empa 25 = subjects randomized to Empagliflozin 25 mg at time of event All Empa = subjects on any randomized dose of Empagliflozin at time of event All Comp = all comparators (placebo, metformin, sitagliptin, glimepiride) N = total number of subjects % = percent of subjects at risk with event										

- We are unable to locate the narrative for patient number 3402 in study 1245.24 with an adverse event of malignant melanoma. Provide us with a narrative of this event or direct us to where this narrative might be found.

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/s/

PATRICIA J MADARA
07/23/2013

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, June 12, 2013 5:18 PM
To: 'daniel.coleman@boehringer-ingenelheim.com'
Subject: NDA 204629 (empagliflozin)
Importance: High
Attachments: 12June13 request for information_attachment.pdf

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We continue to review the data submitted. Please see the attached PDF document containing a request for additional information. Please submit your response officially to the NDA.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Request for Information

To assist in our review of the Empagliflozin new drug application, we request that you provide additional datasets and narratives for analysis of liver events for use with our Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) tool. These datasets should contain the information listed below, and be in the format listed below. The liver test data and the demographic data should include all subjects in the development program. The narrative data does not need to be submitted for all subjects, but is needed for all subjects with liver events, and either ALT > 5xULN or TBL > 2xULN.

We also request that you provide information on potential imbalances in baseline risk factors for lung cancer between the treatment and comparator groups.

Liver Test Data

Requirement	Standardvariable	Variablemeans	Variabletype
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	TRTCD	Treatment Code	Num
Required	TRTGRP	Treatment Group	Char
Required	EXSTDT	Start Date of Dose	Char (ISO 8601 YYYY-MM-DD)
Required	EXDT	Date of Exam	Char (ISO 8601 YYYY-MM-DD)
Required	EXENDT	End Date of Dose	Char (ISO 8601 YYYY-MM-DD)
Required	ALT	Serum alanine aminotransferase activity (U/L)	Num
Required	ALT_REF_HIGH	ALT High Normal Range (U/L)	Num
Required	BILI	Total serum bilirubin concentration (mg/dL)	Num
Required	BILI_REF_HIGH	BILI High Normal Range (mg/dL)	Num
Required	AST	Serum aspartate aminotransferase (U/L)	Num
Required	AST_REF_HIGH	AST High Normal Range (U/L)	Num
Required	ALP	Alkaline phosphatase (U/L)	Num
Required	ALP_REF_HIGH	ALP High Normal Range (U/L)	Num
Optional	ONPROTODC	Subject on Protocol at the Time of exam (Y/N)	Num
Optional	GGT	Gamma glutamyl transferase (U/L)	Num

Demographic Data

Requirement	Standardvariable	variablemeans	Variabletype
Required	STUDYID	Unique identifier for a study within the submission	Char
Required	USUBJID	Unique subject identifier within the submission	Char
Required	INVID	Investigator Identifier	Char
Optional	INVNAM	Investigator Name	Char
Optional	INVDESC	Investigator Description	Char
Required	BIRTHDT	Date of birth	Char (ISO 8601 YYYY-MM-DD)
Optional	AGE	Age in years at randomization	Num
Required	SEX	Sex (M/F)	Char
Optional	RACE	Race (WHITE, BLACK, OTHER)	Char
Optional	COUNTRY	Country	Char
Required	HEIGHT	Height in cm	Num
Required	WEIGHT	Weight in kg	Num
Optional	COMPLETE	Subject completing the study (Y/N)	Char

Optional	DROPDT	Date subject discontinued the study	Char (ISO 8601 YYYY-MM-DD)
Optional	DROPREAS	Reason for discontinuation	Char

Format for Narrative Data:

1. STUDYID (Required): Unique identifier for a study within the submission (Char)
2. USUBJID (Required): Unique subject identifier within the submission (Char)
3. NARRATIVE* (Required): Clinical Narrative (Char)

*: Requirements for Variable NARRATIVE - To the medical writer:

Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hys Law" cases of elevated ALT or AST >3xULN and TBL >2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are:

- 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then
- 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings.

This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug-related liver injury (DILI) be made. Liver biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL >2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH system, as used by medical reviewers at CDER, includes the capability to create time-course graphs for each subject, and to read the narrative summaries, helping them in drawing their own conclusions as to whether the drug may have caused the abnormal findings. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives should be written by physicians or other medical personnel skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives for subjects with either ALT > 5xULN or TBL > 2xULN. The narratives should include information described in the following points:

1. Indication
2. Subject's medical history and concomitant medications
3. Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy
4. Time course of any signs or symptoms of liver disease, including jaundice
5. Differential diagnosis and final diagnosis of liver disease
6. The study site investigator and the sponsor's assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events
7. Clinical course of liver-related adverse events including treatment and outcome
8. Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation.
9. It is also helpful to include in the narrative:
 - Dose and duration of study therapy in weeks
 - Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements

Format of Supplemental Narratives in PDF:

When you submit the clinical narratives in a SAS data set, it should be allowed to supplement narratives in PDF files. Such flexibility should add more power to eDISH in determining potential DILI.

The supplemental narratives can be submitted in the following fashion:

1. Each supplemental PDF file only represents one subject of interest. The name of the PDF file is the unique subject ID: USUBJID that is used in the data submission to the FDA.
2. No two subjects should share the same PDF file.

The supplemental narratives may include any forms of text, bullet points, tables, graphs, or other eye-catching tools that PDF format permits. However, they should be kept simple, clear, and informative.

Important Note for your data manager:

Due to limitations and restriction of the FDA gateway system, the narratives submitted through the FDA gateway system could be truncated. To ensure the FDA reviewer receive complete narratives, please burn the narratives (as SAS data set) and the optional/supplemental narratives on a CD/DVD, and then mail to the review division as a desk copy to compensate such limitations.”

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/s/

PATRICIA J MADARA
06/12/2013

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/s/

PATRICIA J MADARA
06/05/2013



NDA 204629

FILING COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated and received March 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for empagliflozin tablets, 10 mg and 25 mg.

We also refer to your amendment dated April 12, 2013.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is March 5, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: "*Good Review Management Principles and Practices for PDUFA Products*." Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 24, 2014. In addition, the planned date for our internal mid-cycle review meeting is August 26, 2013. We have not yet determined whether we will hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Office of Biostatistics; Division of Biometrics VII

1. Meeting minutes from the data safety monitoring board (DSMB) and DSMB charter for the dedicated cardiovascular outcomes trial, #1245.25, titled “*A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk*”

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

2. Raw electronic data sets for the drug – drug interaction (DDI) study #1245.83, titled “*A randomized, open-label, three-way crossover trial to investigate the effect of rifampicin and probenecid on empagliflozin pharmacokinetics in healthy male and female subjects*”

Please respond only to the above requests for information. 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.

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your requests for a partial waiver of pediatric studies (patients less than 10 years of age) and a partial deferral of pediatric studies (patients greater than nine years of age) for this application. Once we have reviewed your requests, we will notify you if the partial waiver and partial deferral requests are denied.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

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

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/s/

MARY H PARKS
05/16/2013

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, April 18, 2013 12:30 PM
To: 'daniel.coleman@boehringer-ingenelheim.com'
Subject: NDA 204629 (empagliflozin) - request for clarification

Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We have received your application and we are reviewing the data submitted. We have the following comments and requests for clarification:

- **As discussed at the pre-NDA meeting held on November 27, 2012, all laboratory datasets were to be submitted in U.S. units. The same was requested for all tables and figures in the body of individual study reports and in the summaries.**
- **We are unable to identify the laboratory data in U.S. units in your submitted datasets. Additionally, it does not appear that the tables and figures for the individual study reports were converted to U.S. units or hyperlinked to converted tables and figures. In the summaries, it does not appear that the vitamin D data are presented in U.S. units either. If the converted data have been submitted, please provide direction as to where they are located.**

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

PATRICIA J MADARA
04/18/2013

Madara, Patricia

From: Madara, Patricia
Sent: Monday, March 25, 2013 2:40 PM
To: 'daniel.coleman@boehringer-ingelheim.com'
Subject: NDA 204629 - REQUEST FOR INFORMATION
Importance: High
Attachments: Empagliflozin Data Request.pdf

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We have received your application and we are beginning to review the data submitted. Please see the attached PDF document containing requests for additional information. Submit your responses officially to the NDA by April 12, 2013.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Reference is made to your New Drug Application 204629 for empagliflozin tablets, 10 mg and 25 mg, submitted on March 5, 2013. Reference is also made your response, dated March 15, 2013, to our information request regarding the location of the electronic dataset used in the cardiovascular (CV) meta-analysis. In order to conduct our review in a timely manner and produce your results, please submit the following consolidated datasets to your application, based on all trials included in your meta-analysis:

1. Demography dataset: This dataset will contain, at minimum, demography, population indicators, treatment variables, trial dates (e.g. randomization date, start of treatment date, etc.), and measured baseline patient characteristics (e.g. smoking status, history of CV disease, etc.). The structure of this dataset is one record per patient.
2. Disposition dataset: This dataset will have all patient disposition information (e.g. screened, enrolled, treated, discontinued treatment or trial and reasons for discontinuation). The structure of this dataset is one record per patient.
3. Adverse event dataset: This dataset will contain information (including dates) relevant to all adverse events, including CV events, collected during the respective trials. The structure of this dataset will be one record per patient per adverse event.
4. Cardiovascular event committee dataset: This dataset will contain information (including dates) relevant to CV events only. The dataset will include any event that triggers a potential event for adjudication, dates, and whether the event was positively adjudicated for inclusion in the CV analyses. The structure of this dataset will be one record per patient per event.
5. Concomitant medication dataset: This dataset will contain information about all medications administered, including study treatments. The structure of this dataset will be one record per patient per concomitant treatment.
6. Time to Event Analysis Dataset: This dataset will contain all information relevant for the planned time-to CV event analyses. For example, the dataset will contain variables for patient and trial identification, demographics, treatment group, population flags, cardiovascular composite endpoint(s), individual component, censor, and risk factor information. All composite endpoints specified in the meta-analysis protocol (primary, secondary, tertiary), and respective components, as well as all-cause mortality, should be accounted for in this dataset. This dataset will also contain any variable relevant for protocol specified subgroup CV analyses. The structure of this dataset will be one record per patient per analysis population per event.

A sample data definition file summarizing the type of data requested for this dataset is provided in the table that follows; you may create different variables names than those specified. The column labeled "Derivation/Comments" provides clarification of what is

requested for some variables. An example of a partial time to event analysis dataset is also provided.

Dataset Specification: All datasets requested should contain a unique identifier (e.g. USUBJID) for every patient and unique identifier (e.g. STUDYID) for each trial. The patient and trial identifiers should be consistent across all submitted datasets. Submit all requested datasets in SAS transport (.xpt) format.

Submission Content: Submit all of the above requested datasets as well as corresponding complete data definition files. In the data definition files, specify the convention used for missing variables.

Table 1: Sample Time to Event Data Definition File

Time to Event Analysis Dataset: (dataset name).xpt						
Variable Name	Label	Type	Length	SAS Format	Source dataset	Derivation/Comments
USUBJID	Unique subject ID	Char				
STUDYID	Study ID	Char				
SITEID	Site ID	Char				
SUBJID	Subject ID for the trial	Char				
POPLN	Population	Char				Specify analysis population for example, on-study, on-treatment.
TRTP	Planned treatment	Char				
TRTA	Actual treatment received	Char				
DSETRT	Dose of treatment	Char				Specify dosage of treatment (e.g. 30 mg of drug X once daily)
EXPTRT	Duration of treatment exposure (in days)	Num				
RANDDT	Randomization date	Num				
TRTSDT	Date of first exposure to treatment	Num				
TRTEDT	Date of last exposure to treatment	Num				
LASVSDT	Date of last visit	Num				
LASCNDT	Date of last contact ²⁵	Num				
AGE	Age (in years)	Num				
RACE	Race	Char				
BMI	Body mass index (in kg/m ²)	Num				
SEX	Sex	Char				

COUNTRY	Country	Char				
SMOKE	Smoking Status	Char				
DIABDUR	Time since diagnosis of diabetes (in years)	Num				
EVENT	Outcome	Char				Specify (yes or no) if patient experienced each CV outcome (component as well as composite endpoint) and all-cause mortality.
CNSR	Censor	Num				This variable represents if the patient is censored for the corresponding "EVENT" or outcome, described previously. Preferred coding scheme: 1=censored, 0=not censored (event occurred)
EVNTDT	Date of outcome	Num				Specify date of outcome or censor date if patient never has event.
DAYS	Number of days to outcome or censoring	Num				

The partial dataset below provides an example of the content requested for the time to event dataset for a study of duration 90 days. The example is based on information for one patient, ID=12345, who had an MI on day 40 and dies on day 60, due to non-CV causes. The primary MACE endpoint is a composite of MI, stroke or CV death, and the secondary MACE+ endpoint is a composite of MACE or unstable angina. Patient 12345 is on treatment for 15 days and censored 10 days after treatment discontinuation for the on-treatment analysis (as specified in study protocol).

Table 2: Example of Partial Time to Event Dataset for One Patient

USUBJID	POPLN	EVENT	CNSR	DAYS
12345	On study	MI	0	40
12345	On study	Stroke	1	60
12345	On study	CV death	1	60
12345	On study	UA	1	60
12345	On study	MACE	0	40
12345	On study	MACE+	0	40
12345	On study	All-cause death	0	60
12345	On treatment	MI	1	25
12345	On treatment	Stroke	1	25
12345	On treatment	CV death	1	25
12345	On treatment	UA	1	25
12345	On treatment	MACE	1	25
12345	On treatment	MACE+	1	25
12345	On treatment	All-cause death	1	25

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/s/

PATRICIA J MADARA
03/25/2013

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, March 13, 2013 1:58 PM
To: 'daniel.coleman@boehringer-ingenelheim.com'
Cc: Madara, Patricia
Subject: NDA 204629 - REQUEST FOR INFORMATION

Importance: High

NDA 204629

INFORMATION REQUEST

Hi Dan;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin tablets, 10 mg and 25 mg.

We have received your application and we are beginning to review the data submitted. Please see the following comment and request for information below. Please provide your response via email:

- **We are unable to find an electronic dataset to be used in the meta-analysis of cardiovascular safety incorporating cardiovascular safety information across the development program. If such an electronic dataset was submitted, please tell us where to find this dataset within the application.**

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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PATRICIA J MADARA
03/13/2013



NDA 204629

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

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

Name of Drug Product: empagliflozin tablets, 10 mg and 25 mg

Date of Application: March 5, 2013

Date of Receipt: March 5, 2013

Our Reference Number: NDA 204629

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 May 4, 2013, 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.

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

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

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

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>.

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

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
03/11/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 204629

LATE-CYCLE MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director; Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA), dated March 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Jardiance (empagliflozin) tablets, 10 mg and 25 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 2, 2013.

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

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 2, 2013; 2:00 – 3:30 PM
Meeting Location: White Oak Building 22, Conference Room 1419
10903 New Hampshire Avenue
Silver Spring, MD 20903
Application Number: NDA 204629
Product Name: Jardiance (empagliflozin) tablets, 10 and 25 mg
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Chair: Karen M. Mahoney, M.D.
Meeting Recorder: Patricia Madara

FDA Attendees

Office of Drug Evaluation II

Mary H. Parks, M.D. Deputy Director
Sara Stradley, Pharm.D. Administrative Director of Regulatory Affairs

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D. Director (Acting)
Karen M. Mahoney, M.D. Diabetes Team Leader
William Chong, M.D. Medical Officer
Todd Bourcier, Ph.D. Pharmacology/Toxicology Team Leader
Mukesh Summan, Ph.D. Pharmacology/Toxicology Reviewer
Julie Van Der Waag, MPH Chief Project Management Staff
Patricia Madara, M.S. Regulatory Project Manager

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Lokesh Jain, Ph.D. Clinical Pharmacology Team Leader
Manoj Khurana, Ph.D. Clinical Pharmacology Reviewer

Office of Biostatistics; Division of Biometrics II

Mark Rothmann, Ph.D. Team Leader

Office of Biostatistics; Division of Biometrics VII

Mat Soukup, Ph.D. Team Leader
Janelle Charles, Ph.D. Statistics Reviewer

Office of Compliance, Office of Manufacturing and Product Quality; Division of Good Manufacturing Practices

Steve Hertz

Consumer Safety Officer

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)

APPLICANT ATTENDEES

Matthew Bogdanffy, Ph.D.	Director, Nonclinical Drug Safety
Uli Broedl, M.D.	Assoc. Head, Therapeutic Area Metabolism
Daniel Coleman, Ph.D.	Sr. Assoc. Director, Regulatory Affairs
Mark DeBellis, M.S.	Assoc. Director, CMC RA
Stefan Hantel, Ph.D.	Project Biostatistician, Medical Data Services, BI
Kathryn Jason, Ph.D.	Director, Regulatory Affairs
Sabine Jeck-Thole, M.D.	TA Head Risk Management Virology and Metabolism
Gabriel Kim, M.D.	Team Member, Global Pharmacovigilance
Sabine Luik, M.D. MBA.	Sr. VP, Medicine & Regulatory Affairs
Sreeraj Macha, Ph.D.	Team Member, Clinical PK & PD
Roman Messerschmid, Ph.D.	R&D Project Leader
Joanne Palmisano, M.D. FACP	Vice President, Regulatory Affairs
Heidi Reidies, M.S.	Executive Director, Regulatory Affairs
Afshin Salsali, M.D.	Clinical Project Leader, Medicine
Thomas Seck, M.D.	Assoc. Head, Therapeutic Area Metabolism
Mitchell Taub, Ph.D.	Senior Research Fellow, DMPK
Beth Weinberg, R.Ph.	Advisor, Regulatory Affairs, Eli Lilly
Marion Wienrich, Prof., Ph.D	International Project Leader, BI
Markus Wolters, Ph.D.	International Project Leader
Hans-Juergen Woerle, M.D.	Therapeutic Area Head, Metabolism

1.0 BACKGROUND

NDA 204629 was submitted on March 5, 2013 for Jardiance (empagliflozin) tablets, 10 and 25 mg.

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

PDUFA goal date: March 5, 2014

FDA issued a Background Package in preparation for this meeting on November 20, 2013.

2.0 DISCUSSION

LCM AGENDA

1. Introductory Comments – (RPM/CDTL)

Discussion:

FDA reminded the Applicant (Boehringer Ingelheim [BI]) that a final regulatory action had not yet been discussed for Jardiance (empagliflozin) tablets. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting does not address the final regulatory decision for the application.

The Agency reiterated that, at this time, there were no major review issues, no discipline review letters to issue, no advisory committee was planned and no REMS to discuss

2. Discussion of Minor Review Issues

Clinical/Clinical Pharmacology:

- a. Issues which we continue to consider include hepatic safety, malignancy events, the small percentage of Black patients in the development program, and dosing recommendations, particularly in the setting of renal impairment.
- b. We continue to consider the language for the Dosage and Administration. We are considering the following labeling language: (b) (4)

Discussion:

BI asked if there were any requests for information or analyses they could provide in order to facilitate the review process. FDA commented that there was nothing at this time.

The company asked if there was any additional information the Agency could provide regarding dosing in renal patients. FDA commented that internal discussions were continuing but there was no information to share at this time.

3. Additional Applicant Data

Nonclinical

- a. As communicated in our recent teleconference, information relevant to production of the newly identified aldehyde metabolite will be reviewed within the current review cycle. Other remaining new data regarding the mode-of-action proposal will be reviewed at a later date.

Discussion:

FDA noted that there were no additional requests related to the newly identified aldehyde metabolite at this time.

4. Information Requests

- a. An Information Request was submitted by email on November 18, 2013, requesting that the pediatric plan submitted with NDA 204629 be updated to incorporate revisions to the proposed pediatric PK protocol (1245.87)

Discussion:

FDA commented that there may be more information requests as secondary and tertiary reviews were written.

Postmarketing Requirements/Postmarketing Commitments

a.

b.

c.

d.

(b) (4)

Discussion:

FDA commented that there may be additional postmarketing requirements as the review continues.

5. Major labeling issues

- a. Consistent with the advice communicated during the preNDA meeting, section 8.1 of the drug label will indicate ‘pregnancy category C’ and include language similar to the currently approved SGLT2 inhibitor.

b.

(b) (4)

c.

(b) (4)

Discussion:

The Applicant asked if FDA had identified any particular group that would benefit from the 25 mg dose. The Agency stated they had not determined a specific group. The findings would be described in section 14 of the full prescribing information (FPI).

[REDACTED] (b) (4)

t.

FDA commented that this issue would be discussed at the labeling negotiations.

6. Wrap-up and Action Items

Discussion:

BI commented that they would be responding to FDA's request for revisions to the pediatric PK protocol in their pediatric plan.

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/s/

JEAN-MARC P GUETTIER
01/31/2014



NDA 204629

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director, Drug Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for empagliflozin tablets, 10 mg and 25 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 2, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 2, 2013; 2:00 – 3:30 PM

Meeting Location: White Oak Building 22, Conference Room 1419
10903 New Hampshire Avenue
Silver Spring, MD 20903

Application Number: NDA 204629

Product Name: Jardiance (empagliflozin) tablets, 10 and 25 mg

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

Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues

Clinical/Clinical Pharmacology:

- a. Issues which we continue to consider include hepatic safety, malignancy events, the small percentage of Black patients in the development program, and dosing recommendations, particularly in the setting of renal impairment.
- b. We continue to consider the language for the Dosage and Administration. We are considering the following labeling language: (b) (4)

3. Additional Applicant Data

Nonclinical

- a. As communicated in our recent teleconference, information relevant to production of the newly identified aldehyde metabolite will be reviewed within the current review cycle. Other remaining new data regarding the mode-of-action proposal will be reviewed at a later date.

4. Information Requests

- a. An Information Request was submitted by email on November 18, 2013, requesting that the pediatric plan submitted with NDA 204629 be updated to incorporate revisions to the proposed pediatric PK protocol (1245.87)

5. Postmarketing Requirements/Postmarketing Commitments

- a. (b) (4)

b.

(b) (4)

c.

d.

6. Major labeling issues

a. Consistent with the advice communicated during the preNDA meeting, section 8.1 of the drug label will indicate 'pregnancy category C' and include language similar to the currently approved SGLT2 inhibitor.

b.

(b) (4)

c.

(b) (4)

7. Wrap-up and Action Items

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

/s/

JEAN-MARC P GUETTIER
11/22/2013

PeRC PREA Subcommittee Meeting Minutes
November 6, 2013

PeRC Members Attending:

Lynne Yao
Robert Nelson
Hari Cheryl Sachs
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Julia Pinto
William J. Rodriguez
Peter Starke
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Andrew Mosholder
Gregory Reaman
Barbara Buch
Martha Nguyen
Dianne Murphy
Jane Inglese

Guests Attending:

Nichella Simms (PMHS)	Swati Patwardhan (DAAAP)
Erica Radden (PMHS)	Brittany Goldberg (DAVP)
Donna Snyder (PMHS)	Katherine Schumann (DAVP)
Kimberly Compton (DAAAP)	Yodit Belew (DAVP)
Ellen Fields (DAAAP)	Karen M. Mahoney (DMEP)
Srikanth Nallani (DAAAP)	Manoj Khurana (OCP)
Sofia Chaudhry (DPARP)	Lokesh Jain (OCP)
Susan Limb (DRPAR)	
Satjit Brar (OCP)	
Sandy Chang (DPP)	
Glenn Mannheim (DPP)	
Jing Ahang (DPP)	
Lawren Slate (OCP)	
Carla Epps (DGIEP)	
David Joseph (DGIEP)	
Rigo Roca (DAAAP)	
William Chong (DMEP)	
Todd Bourcier (DMEP)	
Josh Lloyd (DAAAP)	
Mukesh Summan (DMEP)	

Agenda

11:00	NDA	204629	Jardiance (empagliflozin) Partial Waiver/Deferral/Plan
11:15	NDA		(b) (4)
11:30	NDA		
11:45	NDA		
	NDA		
	NDA		

Jardiance (empagliflozin) Partial Waiver/Deferral/Plan

- NDA 204629 seeks marketing approval for Jardiance (empagliflozin) for the treatment of Type 2 diabetes mellitus.
- The application was submitted on March 5, 2013, and has a PDUFA goal date of March 5, 2014.
- The application triggers PREA as directed to a new active ingredient.
- A waiver is being requested for pediatric patients aged birth to less than 10 years because studies would be impossible or highly impractical.
- *Division justification for waiver:* The prevalence of type 2 diabetes mellitus in pediatric patients less than 10 years of age is very low, which makes studies in this age range very difficult, if not impossible. Waiver of this age range is consistent with what has been done for other agents for the treatment of type 2 diabetes mellitus.
- A deferral is being requested for pediatric patients aged 10 to less than 18 years because adult studies are completed and the product is ready for approval.
- The sponsor proposes to conduct the following studies:
 - Study 1: PK/PD study in pediatric patients with type 2 diabetes mellitus
 - Protocol Submission: July 31, 2013
 - Study Completion: December 31, 2014
 - Study Report Submission: June 30, 2015
 - Study 2: Safety and efficacy study in pediatric patients with type 2 diabetes mellitus
 - Protocol Submission: September 30, 2014
 - Study Completion: August 31, 2018
 - Study Report Submission: April 30, 2019
- In the Division's view, a more detailed description of the proposed phase 3 trial is not possible at this time. The trial design and sample size estimates are dependent on how many doses are selected for the study, which will be based on the pending PK/PD study.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to less than 10 years because studies are impossible or highly impractical. This age cut off for a waiver has been accepted for all products to treat T2DM to date.

- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 10 to less than 18 years because the product is ready for approval in adults. The PeRC agreed to the proposed timelines for the deferred studies. Clinical efficacy studies are being delayed until non-clinical information related to a renal and bone safety signal can be reviewed.

(b) (4)



IND 102145

MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel Coleman, Ph.D.
Sr. Associate Director, Drug Regulatory Affairs, BIPI
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

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

We also refer to your September 28, 2012, correspondence requesting a Pre-NDA meeting to discuss plans for the submission of a New Drug Application (NDA) for empagliflozin for the treatment of type 2 diabetes.

We also refer to the teleconference between representatives of your firm and the FDA on November 27, 2012. The purpose of the meeting was to plan for the submission of a New Drug Application (NDA) for empagliflozin for the treatment of type 2 diabetes.

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

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, November 27, 2012, 12:00 – 1:00 PM EST
Meeting Location: Teleconference
Application Number: IND 102145
Product Name: Empagliflozin tablets
Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

FDA ATTENDEES

Office of Drug Evaluation II

Leah W. Ripper	Associate Director for Regulatory Affairs, ODE II
Mary H. Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Julie Marchick	Chief, Project Management Staff, DMEP
Pooja Dharia, Pharm.D.	Regulatory Project Manager, DMEP
Lisa Yanoff, M.D.	Clinical Team Leader, DMEP
William Chong, M.D.	Clinical Reviewer, DMEP
Mukesh Summan, Ph.D., DABT	Pharmacology/Toxicology Reviewer, DMEP

Office of Clinical Pharmacology

Lokesh Jain, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Office of Biometrics

Lee Ping Pian, Ph.D.	Biostatistics Reviewer
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SPONSOR ATTENDEES

Matthew Bogdanffy, Ph.D., DABT	Director, Nonclinical Drug Safety
Uli Broedl, Priv. Doz. Dr. Med.	Assoc. Head, Therapeutic Area Metabolism
Daniel Coleman, Ph.D.	Sr. Assoc. Director, Regulatory Affairs
Mark DeBellis, M.S.	Assoc. Director, CMC Regulatory Affairs
Stefan Hantel, Ph.D.	Project Biostatistician, Medical Data Services
Kathryn Jason, Ph.D.	Team Member, Regulatory Affairs
Christina Knieps, Ph.D.	Project Medical Writer, Clinical Operations
Sabine Luik, M.D. MBA	Sr. VP, Medicine & Regulatory Affairs
Sreeraj Macha, Ph.D.	Team Member, Clinical PK & PD
Joanne Palmisano, M.D., FACP	Vice President, Regulatory Affairs
Sandra Raff, M.D. MBA, FACP, FACE	Team Member, Drug Safety
Afshin Salsali, M.D.	Team Member, Medicine

Beth Weinberg, R.Ph.
Marion Wienrich, Prof., Ph.D.
Mitchell Taub, Ph.D.
Carl Busacca, Ph.D.
Donald Tweedie, Ph.D.
Gabriel Kim, M.D.
Roman Messerschmid, Ph.D.
Sabine Pinnetti, M.D.
Iris Deis, Ph.D.

Advisor, Regulatory Affairs, Eli Lilly
International Project Leader, BI
Team Member, Nonclinical DMPK
Distinguished Res. Fellow, Chemical Development
Director, Drug Metabolism and Pharmacokinetics
Co-Team Member Medicine
Team Member, R&D
Team Member, Clinical Operations
Senior Global Regulatory Affairs Manager

1.0 BACKGROUND

Empagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2) and is being developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). SGLT-2 plays an important role in the kidneys and is responsible for most renal glucose reabsorption in T2DM patients. Retention of excess glucose by this pathway contributes to persistent hyperglycemia. Empagliflozin will be available as once-daily 10 mg or 25 mg tablets.

The purpose of this meeting is to discuss:

- the content of a complete application
- Risk Evaluation and Mitigation Strategy (REMS)
- specific FDA requests from the May 22, 2012 FDA comments regarding
 - the CV Safety Study for which a formal clinical trial report will not be available
 - the content, structure, and format for the 4-month Safety Update to the NDA
- BI's proposed submission of new clinical data after the initial submission
- pediatric studies

2. DISCUSSION

1. The chemistry, manufacturing, and controls information will be organized in the ICH Common Technical Document (CTD) format in Module 3 of the NDA.

An overview of the planned CMC documentation to be submitted is provided in Section 10.1. The proposed table of contents of Module 3 is provided in Section 10.2.

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

FDA Response: We have no comments regarding the general organization and/or proposed content to be included in Module 3 of the NDA. For recommendations, we refer you to the ICH guidance M4Q: The CTD-Quality available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf>

Discussion: No discussion occurred.

2. The nonclinical information will be organized in ICH CTD format in Module 4 of the NDA.

The general organization and proposed content of Module 4 is presented in this information package in Section 10.3.

Does the Division have any comments about the general organization and/or proposed content to be included in Module 4 of the NDA?

FDA Response: Please consider the following general guidelines when preparing your submission:

- a. **Final study reports of the nonclinical studies are required at the time of NDA submission. Draft reports would not be acceptable.**
- b. **Histopathology data should include individual animal reports as well as tabulated data that includes incidence and severity scores.**
- c. **Separate summary toxicology tables by species and highlighting drug-related acute, subchronic and chronic study findings, in-life observations, necropsy findings and statistical notation where appropriate.**
- d. **Include a table that specifies the drug batches used in nonclinical and clinical studies, including links to impurity profiles.**
- e. **Nonclinical studies in PDF file format, rather than scanned images of the data, are preferred.**

In addition, we have the following comments regarding reproductive/developmental studies:

- f. **Kidneys of juvenile rats are target organs of toxicity for SGLT-2 inhibitors. Based on review of data for other SGLT-2 inhibitors, there is an increased incidence of dilatation of the renal tubules and pelvi with increased kidney weights in juvenile animals that have not reversed during a recovery period. These adverse effects have occurred without a safety margin to clinical exposure, and are considered secondary to the pharmacological action of SGLT-2 inhibition. Due to differences in timing of kidney development/maturation between rats and humans¹, these adverse effects seen in the kidneys of juvenile rats are considered relevant to the assessment of reproductive and developmental risk for communication in the drug label.**

Standard reproductive toxicology studies with some other SGLT-2 inhibitors have reported similar morphological effects in the kidneys, but the findings have

¹ Suzuki, M (2009) J Toxicol Sci 34;SP267-271 and Zoetis T and Hurtt ME (2003) Birth Defects Res 68;111-120

not been considered indicative of increased human risk based on considerations of incidence, severity, or safety margin to the clinical dose. The substantial difference in the toxicity profile for effects on the kidney between the standard reproductive toxicology studies and juvenile animal studies may reflect exposure to the test-article during a 'critical window' of renal development. The presence of an SGLT-2 inhibitor in fetal tissues and/or in maternal milk of rats is considered sufficient evidence of potential human risk, which would be conveyed in drug labeling.

Empagliflozin is reported to be present in fetal tissues and in maternal milk, and thus presents a potential developmental risk in the second/third trimesters of pregnancy and during nursing. Please include draft language reflecting this risk in Section 8 of the submitted draft label.

- g. Please also see the FDA response to Question 11 regarding chiral inversion of empagliflozin.**

Discussion: No discussion occurred.

3. The clinical information will be organized in ICH CTD format in Module 5 of the NDA.

The general organization and proposed content of Module 5 is presented in this information package in Section 10.4.

Does the Division have any comments about the general organization and/or proposed content to be included in Module 5 of the NDA?

FDA Response: We have no comments regarding the general organization and proposed contents to be included in Module 5 of the NDA. ICH CTD format is acceptable. The general organization and proposed contents of Module 5 are acceptable.

Discussion: No discussion occurred.

4. The ongoing clinical evaluation of safety and efficacy of empagliflozin has not identified any unusual safety concerns which might necessitate a risk evaluation mitigation strategy (REMS). Based on current information, BI does not believe that a REMS is necessary at the time of the application. BI will continue to evaluate data and consider the need based on our findings.

Does the Division have any comments on this plan or on the need for a REMS for this product at the time of the application?

FDA Response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the

benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion: No discussion occurred.

5. This briefing package includes an electronic submissions proposal (Section 10.5) describing technical aspects of the submission, and including identification of CRFs, case narratives, and datasets planned to be included in the NDA.

Does the Division have any comments to this proposal, including comments on the:
Tabular datasets proposed to be included?
Analysis datasets proposed to be included?
Narratives and CRFs proposed to be included?

FDA Response: Your proposal for analysis datasets is acceptable. In addition to the narratives and CRFs that you propose to include, narratives and CRFs for the additional adverse events of interest discussed in item 4(f) of our written responses dated May 22, 2012, should be included. As discussed in item 4(h) of our written responses dated May 22, 2012, present all laboratory data including tables and graphs in U.S. (conventional) units.

BI Response dated 11/27/12: The referenced previous FDA request on May 22, 2012 was:

f. Your adverse events of interest should also include bone health (adverse events of fracture, bone biomarkers if available) and malignancy (including breast cancer and bladder cancer). For malignancy, present analyses separately for patients treated with empagliflozin for greater than six months.

The original application will include additional narratives and CRFs for serious adverse events of fractures, based on a prespecified BI-customized MedDRA query. ***Please confirm that this is adequate.***

FDA Response dated 11/27/12: This is adequate.

Discussion: No discussion occurred.

BI Response dated 11/27/12: Only a restricted set of bone biomarkers (iPTH and 25OH Vitamin D in blood, NTX in urine) was measured in selected trials (1245.33, 1245.20, 1245.31 sub-population continued over from 1245.20, 1245.28) for exploratory analysis, the results are provided with the respective clinical trial reports. No definition of an AE of special interest related to these bone markers was included in the clinical trial protocols or reports, and therefore, the laboratory changes themselves did not automatically lead to a respective documentation of an AE. Therefore we propose to include information on bone biomarkers in case narratives of fractures (as described above) if available. ***Please confirm that this is adequate.***

FDA Response dated 11/27/12: This is adequate.

Discussion: No discussion occurred.

BI Response dated 11/27/12: For malignancy cases, narratives will be provided for all AEs that started after 6 months of study drug exposure (based on SMQ 20000091 and SMQ 20000092). Malignancies will be analyzed as frequency analyses and as patient line listings, separately for all cases and for cases with an onset after 6 months of empagliflozin exposure. ***Please confirm that this is adequate.***

FDA Response dated 11/27/12: This is adequate. However, narratives for all malignancies, i.e. those that occurred prior to 6 months of study drug exposure should be available upon request in a timely fashion.

Discussion: No discussion occurred.

BI Response dated 11/27/12: Laboratory data:

(b) (4)

(b) (4)

FDA Response dated 11/27/12: This is not acceptable. CSRs including all tables and figures should use U.S. units. For example, you should present glucose data in mg/dL (b) (4) for all CSRs, tables and figures.

Discussion: FDA emphasized that all datasets must be submitted in U.S. units. For all pivotal studies (Phase 2 and Phase 3), all tables and figures in the body of the individual CSRs must be in U.S. units or be hyperlinked to supplemental tables and figures which present the data in U.S. units. Tables and figures in the Integrated Summary of Safety should also be presented in U.S. units or be hyperlinked to supplemental tables and figures which present the data in U.S. units. Conversion of other figures or tables to U.S. units may be requested during review of the NDA, and these should be provided in a timely manner.

6. This information package for this meeting (Section 10.6) describes data from the empagliflozin 1245.25 cardiovascular safety study to be included in the NDA, as requested by the Division in the Written Responses dated May 22, 2012, Question 4g.

Does the Division have any comments regarding BI's proposal for the data to be presented from 1245.25?

FDA Response: The proposed safety data to be presented from your ongoing cardiovascular safety study (study 1245.25) is acceptable. As this study is not designed for efficacy, clarify your rationale for submitting the interim efficacy data.

BI Response dated 11/27/12: Overall, efficacy (a prespecified endpoint) was assessed based on the interim cut-off date for CV metaanalysis, on approximately 4500 patients in this study, to ensure the consistency of the results with other phase 3 studies.

A prespecified subpopulation on background of metformin and DPP4 inhibitors (approximately 250 patients) has also been analyzed in order to assess benefit-risk of concurrent use of empagliflozin and DPP4 inhibitors, as DPP4 inhibitors are increasingly used for treatment of patients with T2DM and both safety and efficacy are key concerns for prescribers.

FDA Response dated 11/27/12: This is adequate.

Discussion: No discussion occurred.

- 7. This information package for this meeting (Section 10.7) describes the format and content of the 4 month safety update, as requested by the Division in the Written Responses dated May 22, 2012, Question 5b.

Does the Division have any comments to the safety package proposed to be submitted in the 4 month safety update?

FDA Response: You state that the 4-month safety update will cover subjects in all clinical trials with empagliflozin ongoing from the date of the cutoff for the NDA, but that the majority of the data will be blinded. Clarify what unblinded safety data will be available at the 4-month safety update. It is not clear to us how you will be able to tabulate and summarize these new events and compare the data to the safety profile in the original NDA if the data are blinded.

In addition to case narratives for SUSARs and SAEs of interest, the 4-month safety update should include well-written case narratives for all SAEs.

BI Response dated 11/27/12: The 4-month safety update (4MSU) will cover subjects in all clinical trials with empagliflozin ongoing from the date of the cut-off for the NDA (August 31, 2012), until the date of submission of the NDA.

The following clinical studies will be ongoing during this interval:

Trial No.	Description	Number of Patients (approx)	Blinded at 4MSU cut-off	Interim data in NDA
Unblinded SAE, AESI, and SUSAR narratives, unblinded SAE line listings to be provided				
1245.39	Open label 4-wk acute and chronic effects of empagliflozin on glucose homeostasis in patients	90	N	N

	with IGT and T2DM			
1245.46	Open label 8-week adjunctive to insulin and renal mechanistic pilot trial of empagliflozin in type 1 diabetes patients	42	N	N
1245.53	Open label single 25 mg dose PK/PD study in Japanese type 2 diabetes patients with different degrees of renal impairment	32	N	N
Unblinded SUSAR narratives, blinded SAE line listings provided				
1245.25	Cardiovascular Safety Study	7000	Y	Y
1245.28	104-Week active controlled (Glimepiride) Study	1550	Y	Y
1245.31	52-Week placebo controlled extension of pivotal trials 1245.19, .20, and .23	1856	Y	Y
1245.49	52-Week add-on to insulin in pts. w severe T2DM	550	Y	N
1245.52	52-Week comprehensive add-on study in Japanese patients with T2DM	1070	Y	N
1275.1	52-week factorial design empagliflozin and linagliptin FDC- T2DM patients	2709	Y	N
1276.1	24-Week factorial design study; empagliflozin and metformin FDC- T2DM patients	2718	Y	N
1276.10	16 week BID vs OD comparison study add-on to metformin- T2DM patients	1872	Y	N

No new reports will be available after submission of the NDA to include in the 4MSU. Only the open label studies 1245.53 and 1245.46 will have been clinically completed, but not be fully analyzed, at the cut-off date for the 4MSU. The only new unblinded information for empagliflozin available by the cut-off for the 4MSU will be from these trials.

The 4-month safety update will include line listings for SAEs reported after the cut-off for the original NDA, from the studies listed above (blinded or unblinded, according to the study).

In a brief narrative summary, BI will describe the new unblinded information.

This brief summary and associated tables and narratives will be provided as an amendment to the NDA four months after the submission date, and will be included in Module 5.3.5.3 Reports of analysis of data from more than one study.

FDA Response 11/27/12: This is adequate.

Discussion: No discussion occurred.

8.



Discussion: No discussion occurred.

9.



Discussion: No discussion occurred.

10. In the original NDA submission BI is planning to request a deferral of pediatric studies until the safety and efficacy of empagliflozin has been established in adults. The status of proposed pediatric investigations for empagliflozin currently under discussion with the EMA is described in Section 10.8 of this information package. Pending a decision by the EMA, BI will include in the NDA a proposal for pediatric studies.

Does the Division have any comments on BI's proposed approach for investigating the use of empagliflozin in pediatric patients with type 2 diabetes?

FDA Response: Yes, we agree in general with your plan for a deferral of pediatric studies. However, the request requires review by the Pediatric Review Committee (PeRC) and a decision is not final until the time of approval.

A pediatric plan must be submitted with the NDA and include protocol synopses of the studies you are planning to conduct. The pediatric plan must contain a timeline for the completion of these studies, including the date the final FDA-agreed upon protocol will be submitted, the date studies will be completed, and the date the final study reports will be submitted. See further information below under PREA PEDIATRIC STUDY PLAN.

Discussion: No discussion occurred.

11. The planned content of Module 2 was previously described in the information package for the Type C Meeting (Submission Dated March 1, 2012). All comments from the FDA (letter dated May 22, 2012) will be addressed in the NDA. This pre-NDA information

package provides additional descriptions of the planned content of NDA 204629. The planned contents of each of the technical modules of the NDA are provided in the following attachments to this information package:

- 10.2 Proposed Table of Content of Module 3
- 10.3 Proposed Table of Content of Module 4
- 10.4 Proposed Table of Content of Module 5

Does the Division agree that the proposed contents constitute a complete NDA for empagliflozin?

FDA Response: Refer to our responses to questions 1-3 above. A final decision regarding completeness and fileability of the application will be determined after the NDA is submitted.

(b) (4)





DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

- A preliminary discussion on the need for a REMS was held. Please see Question 4.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the

following minor application components may be submitted within 30 calendar days after the submission of the original application:

-  (b) (4)

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 204629: LATE COMPONENT – CLINICAL PHARMACOLOGY**

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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

/s/

POOJA DHARIA
12/17/2012



IND 102,145

MEETING MINUTES

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

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 10733 XX Tablets.

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on May 4, 2010.

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, call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

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

Enclosure: Meeting Minutes

CHEMISTRY MANUFACTURING CONTROLS AND BIOPHARMACEUTICS

Revised Question 3

BI developed the final formulation for BI 10773 tablets for use in all Phase 3 trials scheduled to start in 2010 and later. In addition, trial 1245.33, a 78-week trial of BI 10773 and placebo in patients being treated with basal insulin with or without concomitant metformin and/or sulfonylurea, started in late 2009, is being carried out with the Phase 2 formulation tablets (protocol submitted to IND 102,145 October 29, 2009/SN 0023). Data indicate that BI 10773 is a BCS Class III compound (see Item 10.1).

(b) (4)

Is it required to bridge the two formulations in this case?

(b) (4)

PRE-MEETING COMMENTS:

FDA: No, (b) (4) is not acceptable. (b) (4)

(b) (4)

SPONSOR'S RESPONSE: Per your request, BI plans to provide the final bioequivalence protocol for review in early 3Q 2010, with a goal of initiating the trial by approximately the end of 3Q 2010. Your timely feedback would be appreciated.

MEETING DISCUSSION:

(b) (4)

CLINICAL PHARMACOLOGY

Revised Question 8

In response to FDA's December 8, 2009 comments to Question 8 of the EOP2 meeting package, the analysis of the currently available data for BI 10773 interaction with pioglitazone, and literature information concerning gemfibrozil is in Item 10.2.

Does the FDA agree with our analysis of the currently available data? As such, what is the rationale for the FDA's recommendation to conduct a clinical DDI study with BI 10773 and gemfibrozil?

PRE-MEETING COMMENTS:

FDA:

Your drug interaction study results between BI 10773 and pioglitazone is one example of the uncertainty involved with the mechanism for BI 10773's DDI potential with other drugs. We do not believe that one particular DDI study can explain all the uncertainty involved in BI 10773's DDI potential, however, the gemfibrozil interaction study with BI 10773, which we have recommended may illustrate the "worst case" of DDI potential with BI 10773 for the following reasons:

- BI 10773 is mainly metabolized by UGT and gemfibrozil is known to inhibit glucuronidation. You noted that "gemfibrozil does not inhibit the major human UGT enzymes responsible for glucuronidation" (Goosen *et al.*, 2007). However, the report utilized only atorvastatin as a substrate, and we do not agree that this result can be extrapolated to other substrates because the inhibition potential of gemfibrozil on glucuronidation is dependent on substrates and gemfibrozil concentrations (Prueksaritanont *et al. J Pharmacol Exp Ther.* 2002 Jun;301(3):1042-51).
- Contrary to your notion that gemfibrozil is metabolized primarily by UGT2B7, various UGT isozymes are reported to be involved in gemfibrozil glucuronidation (i.e., 1A1, 1A3, 1A9, 2B7, and 2B17, Prueksaritanont *et al. J Pharmacol Exp Ther.* 2002 Jun;301(3):1042-51). Therefore, it is difficult to identify the relative contribution of each UGT isozyme to the inhibition of glucuronidation by gemfibrozil if multiple isozymes are involved in glucuronidation.
- BI 10773 is a substrate of transporters such as P-gp and OATP, and gemfibrozil is known to inhibit transporters such as OATP. Therefore, there might be a synergistic effect of gemfibrozil on BI 10773 exposure through inhibition of both metabolism and transport.
- Gemfibrozil will likely be co-prescribed with BI 10773 in clinical practice.

SPONSOR'S RESPONSE: Because it is likely that gemfibrozil and BI 10773 could be co-prescribed, we are considering the appropriate study design. We would like to discuss the objective of the study at the EOP2 meeting.

MEETING DISCUSSION: FDA clarified that the purpose of this drug interaction study is to assess the effects of gemfibrozil on the pharmacokinetics of BI 10773.

New Drug Interaction Question 8a

(b) (4)

PRE-MEETING COMMENTS:

FDA:

(b) (4)



SPONSOR'S RESPONSE:

(b) (4)



(b) (4)



MEETING DISCUSSION: *None.*

CLINICAL

Revised Question 12

Final data from the 12-week Phase 2 trials of BI 10773 and from the Phase 1 pharmacokinetic trial of BI 10773 in patients with renal impairment are in Items 10.4, 10.5, 10.6.

Does FDA concur with the selection of BI 10773 10 mg and 25 mg as once daily doses to be tested in Phase 3 studies? (see Phase 3 protocol synopses in Item 10.7)

PRE-MEETING COMMENTS:

FDA: Yes

MEETING DISCUSSION: *None.*

Revised Question 17

The ECG collection proposal for Phase 1-3 studies is in Item 10.9. Does FDA have any comments on the plan?

PRE-MEETING COMMENTS:

FDA:

We note that you are not planning to have electrocardiograms (ECGs) reviewed centrally by cardiologists. This is acceptable, but if a safety signal relevant to ECGs emerges, you will be required to reevaluate ECGs centrally. Your thorough QT study proposal will be forwarded to the FDA's Interdisciplinary Review Team (IRT) for QT Studies for review. Please submit the QT study protocol to the Division with sufficient time before your planned protocol initiation to allow time for the IRT to review your protocol.

SPONSOR'S RESPONSE:

Per your request, BI plans to provide the final QT study protocol for review in June, 2010, with a goal of initiating the trial approximately two months later. Your timely feedback would be appreciated.

MEETING DISCUSSION: *None.*

Revised Questions 18, 19, 20, and 21.

Updated protocol synopses in Item 10.7 incorporate FDA comments and BI revisions for trials 1245.19, 1245.20, 1245.23, and 1245.28.

A clarification of the glimepiride doses to be used in trial 1245.28, and the proposal for ensuring that patients are at maximal or near-maximal doses of glimepiride is in Item 10.8.

Does FDA have any additional comments on these protocols?

PRE-MEETING COMMENTS:

FDA:

We have reviewed your rationale for using the 4 mg dose of glimepiride in trial 1245.28. We do not fully agree that results from the two referenced short-term trials adequately reflect glycemic efficacy of 4 mg vs. higher glimepiride doses over the duration of a 2-year trial. If you titrate to only 4 mg of glimepiride, please be aware that any labeling language regarding this protocol will clearly reflect the fact that the maximal dose of

glimepiride was not used, which could affect claims of superiority or non-inferiority. See the recently approved liraglutide package insert for an example of how a submaximal dose of glimepiride comparator was labeled.

FDA: Please confirm that the run-in period for submaximal/maximal doses of the background therapies is of sufficient duration for all phase 3 protocols to ensure that glycemic control is accurately reflected in the baseline HbA1c measurement.

SPONSOR'S RESPONSE: Phase 3 protocols with background therapy will require 12 weeks on stable dose before entry.

FDA: Trial 1245.19 does not explicitly state that pioglitazone will *not* be uptitrated during the trial (as trial 1245.23 indicates for its background therapies). Please confirm that background pioglitazone doses will remain stable throughout the trial.

SPONSOR'S RESPONSE: Yes, stable background (no change during trial) will be specified in the protocol.

FDA: Trial 1245.20 indicates that a key secondary endpoint will be change of body weight >-2%. The Division views a 2% weight loss as a clinically irrelevant endpoint which would be unlikely to be accepted into labeling. A weight loss cutoff of 5% is typically used for obesity drug labeling. Alternatively, a comparison of mean body weight change in each group could be the key secondary endpoint.

SPONSOR'S RESPONSE: The key secondary endpoint is mean change in body weight at 24 weeks; the -2% is part of an exploratory composite endpoint, not a key secondary endpoint.

FDA: Randomization stratified by background therapy is recommended for trial 1245.19 and trial 1245.23.

SPONSOR'S RESPONSE: This will be addressed in the protocols.

FDA:

(b) (4)
(b) (4)

SPONSOR'S RESPONSE: We understand the position. No additional response.

FDA: In handling missing observations, you should also apply Multiple Imputation and MMRM.

SPONSOR'S RESPONSE: Yes, that will be specified in the protocols.

FDA: Baseline treatment comparisons should be made corresponding to endpoint (efficacy) treatment comparisons.

SPONSOR'S RESPONSE: We propose to make the comparisons for the primary and key secondary endpoints.

MEETING DISCUSSION: None.

Revised Question 22

Revisions to the proposal for assessment of BI 10773 in patients with type 2 diabetes and renal impairment (trial 1245.36) is in Item 10.7, (b) (4)

(b) (4)

Does FDA agree (b) (4)

(b) (4)

PRE-MEETING COMMENTS:

FDA:

Clarify the anticipated drop-out rate for patients participating in Study 1245.36.

Your drug acts directly on the kidney, raising unique safety and efficacy concerns in patients with renal impairment. Therefore, we do not agree with your plan (b) (4)

(b) (4) The full study report for the one year of treatment should be submitted with the original NDA.

The protocol synopsis permits background metformin use. However, metformin is contraindicated in these patients.

SPONSOR'S RESPONSE:

The anticipated overall drop out rate for study 1245.36 is 5%. Metformin will be allowed according to local labeling.

MEETING DISCUSSION: FDA stated that the 5% dropout rate in the renal impairment study seems low. The Sponsor stated that 5% is based on its experiences in other renal impairment trials. With regard to metformin use, the sponsor clarified that some countries permit use of metformin in patients with mild renal impairment.

Revised Question 24

(b) (4)

PRE-MEETING COMMENTS:

FDA:

The once daily dose of BI 10773 that will be compared to metformin is not specified.

SPONSOR'S RESPONSE:

The treatment groups in 1276.1 are	
BI 10773 25 mg qd	N=357
BI 10773 12.5 mg + Met 500 mg bid	N=135
BI 10773 12.5 mg + Met 850 mg bid	N=135
BI 10773 12.5 mg + Met 1000 mg bid	N=135
Met 500 mg bid	N=135
Met 850 mg bid	N=135
Met 1000 mg bid	N=357

With this information, can FDA respond to the question

(b) (4)

MEETING DISCUSSION: FDA stated that the sponsor's plan appears to

(b) (4)

Revised Question 25

Protocol 1245.25 has been revised to address the comments from the December 8 FDA letter. A revised meta-analysis proposal is in Item 10.11, and the protocol for trial 1245.25, is in Item 10.12.

Does the agency have any additional comments on the proposal for trial 1245.25, or on the proposed meta-analysis for assessment for cardiovascular risk?

PRE-MEETING COMMENTS:**FDA:**

In the December 8 letter, we asked you to "... perform a sample size calculation with respect to the 1.3 non-inferiority margin and propose a plan for collecting adequate numbers of primary CV events to rule out this hazard ratio". Your proposal evaluates the 1.3 margin at the interim and final analyses using a sequential test of that boundary after first testing the 1.8 margin. The power of the tests of the 1.3 margin after 60 and 152 events, the expected analysis times, is only about 11% and 25%, respectively, assuming $\alpha = .0141$ (one-sided) and the true hazard ratio is 1.0 at each analysis. Furthermore, the CV protocol 1245.25 will stop at 102 primary events (protocol, p. 59). Given you are unlikely to rule out the 1.3 margin after 60 and 152 events, please provide us with a full development plan that has adequate statistical power to rule out a risk/hazard ratio of 1.3.

There are two planned meta-analyses, including one interim analysis, to evaluate CV risk after 60 CV events and again "when the finally decided number of events have been observed" (meta-analysis plan, p.15). It appears you will potentially increase the number the target final number of events (152) based on the hazard ratio observed at the interim analysis. (A decrease in the target number of events would constitute a second interim

analysis.) This adaptation will require further changes to the alpha of .0141 assigned to the final analysis or down-weighting the additional event data, and simulations to determine the precise alpha adjustment. A more transparent and less conservative alternative would define the analysis times by the pre-specified event totals of 60 and 152.

Please comment on the rationale for the different primary endpoints for the CV study and CV meta-analysis, the latter which will include CV study events.

If your proposed CV trial is only designed with adequate power to rule out the 1.8 margin, clarify the rationale for submitting interim data from this trial at NDA submission as opposed to waiting until the trial is completed. In addition, clarify whether you are planning to update your cardiovascular analyses for the 4 month safety update.

SPONSOR'S RESPONSE: BI would like to address the Division's comments at the meeting. We plan to present 1-2 slides depicting the cardiovascular strategy.

FDA: "Study" factor should be included in the model

SPONSOR'S RESPONSE: It will be included.

FDA: What is the rationale for the requirement BMI ≥ 27 kg/m²?

SPONSOR'S RESPONSE: The requirement for BMI ≥ 27 kg/m² was included in the previously submitted meta-analysis for body weight, which is no longer planned. Trial 1245.25 requires a BMI ≤ 45 kg/m².

FDA: In an alternative analysis, include only patients who were on treatment for an adequate amount of time to have CV events due to the test drug.

SPONSOR'S RESPONSE: Does the Agency have a suggestion for the appropriate length of time patients should be on study treatment for inclusion in this analysis?

MEETING DISCUSSION:

The CV program overview depicted in the Sponsor's powerpoint slides suggested an unblinded interim analysis at the end of Phase 3 prior to the designated interim and final analyses of CV events currently scheduled at 60 and 152 events. This analysis will be performed without adjustment of type 1 error. FDA stated that any contemplated action or design change based on this early analysis of study results must be accompanied by a prospective type 1 error penalty.

Due to the low statistical power to rule out the 1.3 non-inferiority margin, the sponsor was asked about plans to collect CV data after approval in the event 1.8 is ruled out but 1.3 is not. The sponsor was asked about any plans to extend the dedicated CV study beyond its

current planned duration of 102 events. This option was discussed as was an option involving a second CV study in a slightly different population. No decision was reached on which option, if any, would be pursued.

FDA stated that the sponsor's statistical plan is unclear. FDA also expressed concerns about certain statistical approaches, particularly study adaptations based on un-blinded interim data. Currently, the division is discouraging the use of some adaptive designs, such as the proposed adaptation of increasing the sample size (i.e., number of CV events) beyond the pre-specified event totals based on an interim estimate of the hazard ratio in the assessment of cardiovascular risk. This type of adaptation falls into a class of adaptations categorized by the Office of Biostatistics as designs whose properties are not fully understood. (See January 2010 draft "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics"). Therefore, FDA requested that the sponsor submit a revised CV analysis plan based on a more conventional design that more fully addresses the 1.8 and 1.3 non-inferiority margins. An example of a more conventional design would be one in which interim (and final) analyses with respect to the 1.8 and 1.3 margins are performed, with appropriate control of type 1 error, at pre-specified information times determined by the total number of CV events in the two treatment groups. The Division stated that CV approaches based on adaptive designs like those mentioned above may be possible but stated that those approaches are complex and detailed proposals would need to be fully vetted with FDA prior to implementation.

FDA stated that if the pre-approval cardiovascular trial is adequately powered to only meet the 1.8 margin then complete data (not interim data) from this trial should be included at the time of NDA submission. If the trial is adequately powered to meet the 1.3 margin then it is acceptable to use interim data from the trial to meet the 1.8 margin at the time of NDA submission while continuing the trial to accrue data to eventually meet the 1.3 margin.

With regard to how long patients should be on study treatment for inclusion in a supportive analysis of cardiovascular safety, FDA stated that we do not have a clear answer for this. The sponsor can submit a proposal with rationale for review.

Question 26 - New

As requested in the December 8 Advice from FDA, narratives for patients who reported adverse events compatible with transaminitis in the Phase 2 trials, and a summary of the findings, are provided in Item 10.13.

Does FDA have any additional comments on these data?

PRE-MEETING COMMENTS:

FDA:

No additional comments at this time.

MEETING DISCUSSION: *None.*

OTHER PRE-MEETING COMMENTS:

FDA: Clarify whether rhabdomyolysis was diagnosed in any of the BI 10773-treated patients in the phase 2 program who developed increased creatine phosphokinase.

SPONSOR'S RESPONSE: No patient has been diagnosed with rhabdomyolysis in BI 10773 trials to date.

FDA: There appear to be inaccuracies in your exposure tables (Section 10.10). For example, you report 108 patients in Study 125.36 will have estimated creatinine clearance <30 mL/min yet the "total" row shows only 30 such patients. In addition, clarify whether the patient exposures in the 4 sets of exposure tables reflect all randomized patients or only BI 10773-treated patients. If all randomized patients, please submit updated tables showing the data for only BI 10773-treated patients.

SPONSOR'S RESPONSE:

The submitted tables reflect only BI 10773 treated patients.

The columns for number of patients with severe renal impairment were incorrect.

The numbers will be revised to reflect the inclusion of final data from 1245.36 into the NDA according to the requirement in response to Question 22.

FDA: For your exposure tables (Section 10.10), clarify whether you intend to submit blinded or unblinded interim data from ongoing studies at NDA submission and at the 120-day safety update.

SPONSOR'S RESPONSE: The interim data will be unblinded.

FDA: You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

MEETING DISCUSSION: *None.*



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: [Identify type of meeting, such as A, B, C]
Meeting Category: [Identify category of meeting, i.e., Pre-IND, End of Phase 2, Pre-NDA, etc.]

Meeting Date and Time: [Insert meeting date and time]
Meeting Location: [Insert meeting location]

Application Number: [Insert application number]
Product Name: [Insert product name]
Indication: [Insert indication]
Sponsor/Applicant Name: [Insert sponsor name]

Meeting Chair: [Insert the meeting leader's name.]
Meeting Recorder: [Insert the meeting recorder's name.]

FDA ATTENDEES

Name 1, Title, Division/Office
Name 2, Title, Division/Office
Name 3, Title, Division/Office

SPONSOR ATTENDEES

Name 1, Title (and affiliation if not the sponsor)
Name 2, Title (and affiliation if not the sponsor)
Name 3, Title (and affiliation if not the sponsor)

1.0 BACKGROUND

[The background section should contain the following information to set a context for the meeting:

Provide a brief history of events leading up to this meeting, including but not limited to previous decisions and actions

Context for product development. This should include providing a brief description of any protocols to be discussed at the meeting and not just a reference to the description of the protocol in the briefing package or previous meeting minutes.

Purpose for this meeting

Describe expected outcome for meeting

2. DISCUSSION

[Recommend, if appropriate, to organize questions by categories and/or disciplines. Each category and/or discipline receives a subheading. Insert each question submitted by sponsor. In unusual cases where there are not specific questions and answers, substitute agenda topics with a brief description of each]

2.1. Category/Discipline A

Question 1: [Insert the question the sponsor submitted to the FDA. Clearly identify the sponsor question from the FDA response. If you decide to use a different font or formatting style, then remember to be consistent throughout the document.]

FDA Response to Question 1: [Insert the response by FDA to the question submitted. Refer to the Best Practices Writing and Style Guide for Meeting Minutes Content for helpful hints]

Discussion:

[Insert any discussion points that occurred during the meeting or teleconference related to the above question and/or response. Other points to remember include:

- The discussion should not be presented verbatim and capture only salient and relevant points.
- The summary of the discussion should clearly identify which party, either FDA or sponsor, owned the discussion point. The discussion should not identify individuals.
- If there was no discussion and the sponsor accepted the response as is, then insert a comment, such as, "The sponsor accepted FDA's response, no discussion occurred."
- Clearly identify agreements and/or disagreements that were reached by FDA and the sponsor during the discussion related to the specific question.

2.2. Category/Discipline B

[Repeat the same structure as identified under Section 2.1 for each question (or topic) related to category/discipline B.]

3.0 ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

4.0 ACTION ITEMS

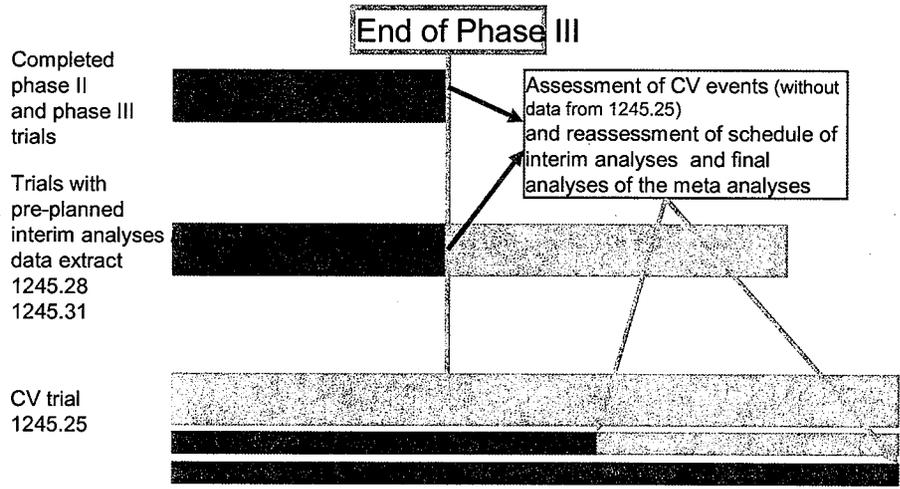
[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
[Insert action item with a brief description, if applicable]	FDA	[Insert date]
[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

5.0 ATTACHMENTS AND HANDOUTS



Overview of ongoing and completed trials at time of anticipated submission 



Schedule of Analyses to Assess Cardiovascular Safety of BI 10773

04-MAY-2010
 2

Overview of CV Analyses 

Analyses	Included trials
Assessment of CV events at end of phase III Based on the results, the interim analysis and final analysis of the meta-analysis including 1245.25 will be re-scheduled (re-definition of number of events)	Completed phase II / III trials and interim analysis of 1245.28 and 1245.31
Interim analyses of CV Meta-Analysis	Completed phase II / III trials, interim analysis of 1245.28 and 1245.31 and data extract from 1245.25
Final Meta-Analysis	Completed phase II / III trials, interim analysis or final analysis of 1245.28 and 1245.31 and final analysis of 1245.25

Schedule of Analyses to Assess Cardiovascular Safety of BI 10773

04-MAY-2010
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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

.ND-102145

GI-1

BOEHRINGER
INGELHEIM

BI 10773 XX Tablets

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

/s/

MARY H PARKS

06/03/2010