CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208658Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208658 SUPPL # HFD # 510

Trade Name Synjardy XR

Generic Name empagliflozin and metformin hydrochloride extended-release

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known December 9, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☐ NO ☒

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

This NDA did not include new clinical data to investigate the efficacy of empagliflozin and metformin XR fixed dose combination. The two new studies that were included in this application are both phase 1 bioequivalence studies:

1276.15: Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (25 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)

1276.28: Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (10 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)

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:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 206111	Synjardy (empagliflozin and metformin hydrochloride) tablets
NDA# 204629	Jardiance (empagliflozin) tablets
NDA# 021748	Glumetza (metformin hydrochloride extended-release) tablets

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

IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☐ NO ☒

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

The application proposes an extended-release version of a previously approved product (Synjardy NDA206111).

No Phase 3 clinical trials were conducted in this NDA. The applicant is relying on two pivotal phase 1 bioequivalence bridging studies (studies 1276.15 and

1276.28), along with existing clinical safety and efficacy data from:
• Empagliflozin (Jardiance; NDA 204629),
• Empagliflozin/metformin IR (Synjardy NDA 206111),
• Metformin XR (Glumetza NDA 021748).

(b) (4)

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Michael G. White, Ph.D.
Title: Regulatory Project Manager
Date: December 9, 2016

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

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

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

/s/

MICHAEL G WHITE
12/09/2016

JEAN-MARC P GUETTIER
12/09/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208658 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Synjardy XR Established/Proper Name: empagliflozin and metformin hydrochloride extended-release Dosage Form: tablets		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Michael G. White, PhD		Division: Division of Metabolism and Endocrinology Products

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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

❖ Actions	
• Proposed action • User Fee Goal Date is December 10, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

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

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

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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP: December 9, 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Final labeling attached to approval letter dated 12/09/2016
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Final labeling attached to approval letter dated 12/09/2016
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Final labels attached to approval letter dated 12/09/2016
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letter: 05/05/2016 Review: 04/22/2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 04/15/2016 DMEPA: ☐ None 11/21/2016 11/14/2016 10/14/2016 DMPP/PLT (DRISK): ☐ None 12/02/2016 OPDP: ☐ None 12/05/2016 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	03/25/2016 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 09/28/2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Labeling: 12/08/2016 Labeling: 12/07/2016 Labeling: 12/06/2016 Labeling: 11/23/2016 Advice: 11/15/2016 Advice: 11/09/2016 Advice: 11/01/2016 Advice: 10/18/2016 Info Request: 09/30/2016 (2) Info Request: 07/18/2016 No filing issues letter: 04/20/2016 Ack NDA letter: 02/17/2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Granted as Written Responses at Sponsor's Request: 07/16/2015
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None See CDTL review
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/02/2016
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review See CDTL Review above dated 12/02/2016
• Clinical review(s) *(indicate date for each review)*	Review:12/02/2016 Filing: 04/20/2016
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	12/02/2016 See Clinical Review, pages 12, 24, & 25
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None Review: 11/03/2016 Filing: 04/08/2016

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

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Review: 11/03/2016 Filing: 04/12/2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested Review: 10/24/2016 Review: 07/08/2016 Review: 05/27/2016 Memo: 05/17/2016
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Review: 11/07/2016 Filing: 03/23/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 11/03/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/03/2016 See Integrated Quality Assessment, Chapter II: Drug Product, page 26
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

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

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 11/03/2016, See Integrated Quality Assessment, Chapter VI: Facilities Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

---

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

/s/

MICHAEL G WHITE
12/09/2016

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA 208658, "Synjardy XR": 3rd Round FDA DRAFT LABELING
Date: Thursday, December 08, 2016 4:34:29 PM

Dear Mike,

Thanks, received.

BR, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, December 08, 2016 4:32 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: NDA 208658, "Synjardy XR": 3rd Round FDA DRAFT LABELING

Dear Joachim,

Attached are the third round of FDA edits of the draft labeling for the Prescribing Information (PI) and Medication Guide for NDA 208658, empagliflozin and metformin hydrochloride extended-release tablets (Synjardy XR). These edits reflect changes made to the labeling that was received from you via email on December 8, 2016. We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

We ask the you complete your review and return comments as soon as possible or by 11am**, Friday, December 9, 2016.**

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

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149

Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

---

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

/s/

MICHAEL G WHITE
12/08/2016

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA 208658 SYNJARDY XR 2nd round of labeling comments
Date: Wednesday, December 07, 2016 3:55:27 PM
Attachments: image001.png

Dear Mike,

Received, thanks.

BR, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Wednesday, December 07, 2016 3:51 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: RE: NDA 208658 SYNJARDY XR 2nd round of labeling comments

Hi Joachim,

Thank you for your email and the attention that you brought to the lactic acidosis language in the draft Medication Guide for NDA 208658, Synjardy XR. I have the following clarifications/requests for you from the review team. Please don't hesitate to contact me if you have any questions.

(1) Please disregard the edits on the lactic acidosis section of the Med Guide; these were incorrect (all other edits to the Med Guide were correct). The Synjardy XR med guide language on lactic acidosis should align with the Synjardy med guide lactic acidosis language for the metformin Safety Labeling Change approved on July 8, 2016.

(2) Please also make the following change to Highlights of the Prescribing Information, Drug Interactions;

- **Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine), may increase the accumulation of metformin. Consider the benefits and risks of concomitant use (7.2)**

This will align HL with the revised text in 7.2 sent to you on 12/6.

Thank you!

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Wednesday, December 07, 2016 8:35 AM
To: White, Michael G (CDER)
Subject: NDA 208658 SYNJARDY XR 2nd round of labeling comments

Dear Mike,

I would like to reach out to you for clarification of the lactic acidosis language in the Medication Guide that was provided by the Division in the 2nd round of labeling comments.

Would you please confirm that the language that is provided in the 2nd round of labling comments for Synjardy XR is correct?

It seems to be inconsistent with the Metformin SLC letter received in April, and also with labeling for approved products, including Synjardy.

If possible, please provide your feedback by as soon as possible / by today.

Thanks and BR,

Joachim.

Boehringer Ingelheim

Dr Joachim Troost
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5155 :: (b) (6)
joachim.troost@boehringer-ingelheim.com

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

/s/

MICHAEL G WHITE
12/07/2016

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA 208658, "Synjardy XR": 2nd Round FDA DRAFT LABELING
Date: Tuesday, December 06, 2016 5:09:09 PM

Dear Mike,

Receipt confirmed. Thanks, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, December 06, 2016 5:08 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: NDA 208658, "Synjardy XR": 2nd Round FDA DRAFT LABELING

Dear Joachim,

Attached are the second round of FDA edits of the draft labeling for the Prescribing Information (PI) and Medication Guide for NDA 208658, empagliflozin and metformin hydrochloride extended-release tablets. These edits reflect changes made to the labeling that was received from you via email on November 30, 2016. We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

We ask the you complete your review and return comments as soon as possible or by the opening of business**, Thursday, December 8, 2016 (by 9am EST).**

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

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

---

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

/s/

MICHAEL G WHITE
12/06/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208658

LABELING PMR/PMC DISCUSSION COMMENTS

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated February 10, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for empagliflozin and metformin hydrochloride extended-release tablets.

We also refer to our April 20, 2016, letter in which we notified you of our target date of November 12, 2016, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On November 14, 2016, we received, via email, your most recent proposed Prescribing Information (PI) and Medication Guide labeling for this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by November 30, 2016. The resubmitted labeling will be used for further labeling discussions.

Please be aware that portions of this label are still under review and consideration.

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

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

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

If you have any questions, call me at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Michael G. White, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Round 1 FDA Draft Labeling for NDA 208658

White, Michael G (CDER)

To: joachim.troost@boehringer-ingelheim.com
Subject: NDA 208658, "Synjardy XR": 1st Round FDA DRAFT LABELING
Attachments: NDA208658 Labeling PMR-PMC Discussion Comments.pdf; NDA208658 labeling FDA Rnd 1 Nov 23 2016.doc

Dear Joachim,

Attached are the first round of FDA edits of the draft labeling for the Prescribing Information (PI) and Medication Guide for NDA 208658, empagliflozin and metformin hydrochloride extended-release tablets. These edits reflect changes made to the labeling that was received from you via email on November 14, 2016. In addition, because an action is pending on the supplemental application NDA 206111/S-004, we request that language related to the (b) (4) be removed from this label. We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

We ask the you complete your review and return comments as soon as possible or by the opening of business**, Wednesday, November 30, 2016 (by 9am EST).**

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

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

---

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

/s/

MICHAEL G WHITE
11/23/2016

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA 208658, Synjardy XR: Comments on CARTON & CONTAINER LABELING
Date: Tuesday, November 15, 2016 8:56:17 AM

Dear Mike,

Receipt confirmed, thanks.

Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, November 15, 2016 8:17 AM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: NDA 208658, Synjardy XR: Comments on CARTON & CONTAINER LABELING

Dear Joachim,

We have the following comments and recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) pertaining to your carton and container labels submitted on November 9, 2016, for NDA 208658.

Please note that we may have additional comments later.

In order to increase the readability and prominence of important information in the proposed labels to clarify information and mitigate any confusion that may interfere with the safe use of Synjardy XR, we recommend the following:

A. Container Label-Commercial

1. For each of the labels for the 30 tablet package size, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the other container labels to read: "Store at 25°C (77°F); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

B. Container Label-Professional Sample

1. For each of the labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the commercial container labels to read: "Store at 25°C (77°F); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

Please resubmit any updated labeling with applicable changes.

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

Kind regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

/s/

MICHAEL G WHITE
11/15/2016

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING
Date: Wednesday, November 09, 2016 5:52:27 PM
Attachments: image001.png

Dear Mike,

Thanks for the quick turnaround – receipt confirmed.

Thanks, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Wednesday, November 09, 2016 4:06 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Joachim,

Please refer to your email dated November 9, 2016, in response to our email dated November 1, 2016, pertaining to the labeling for NDA 208658. You proposed the following wording regarding the storage conditions in the Prescribing Information and Medication Guide:

> "…
>
> US PI, Section 16
> *Storage*
> **Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)** [see USP Controlled Room Temperature]. Store in a safe place out of reach of children.
>
> Medication Guide
>
> **How should I store SYNJARDY XR?**
> Store SYNJARDY XR at room temperature 68°F to 77°F (20°C to 25°C).
>
> …"

The Division of Medication Error Prevention and Analysis (DMEPA) finds your proposed wording acceptable.

Please confirm receipt and let me know if you have any questions,

Kind regards,

-Mike
Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Wednesday, November 09, 2016 1:53 PM
To: White, Michael G (CDER)
Subject: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Mike,

As previously indicated (please see our email from November 11, 2016, providing updated proposed labeling), we further evaluated the implementation of DMEPA's response (see below in bold) for US PI and Medication Guide.

"we agree with your proposal to use the phrase "Store at 25°C (77°F)" on the Commercial and Professional Sample versions of your Carton and Container labeling for NDA 208658. Please remember that this statement should be the same for consistency between all of the labeling and labels, including in the Medication Guide."

BIPI Response:
BIPI's currently proposed wording regarding the storage conditions in US PI and Medication Guide is as follows:

"…

US PI, Section 16
Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Store in a safe place out of reach of children.

Medication Guide

How should I store SYNJARDY XR?
Store SYNJARDY XR at room temperature 68°F to 77°F (20°C to 25°C).

…"

While BI strongly supports efforts for consistency across all labeling, we continue to consider the currently proposed wording regarding the storage conditions in the US PI, Container Label, and the Medication Guide as appropriate given that this labeling is intended to communicate the recommended storage conditions to different audiences.

The information provided in Section 16 of the US PI, and Container Label, is intended to inform health care providers on storage conditions according to scientific standards for quality [definition of Controlled Room Temperature, USP General Notices and Requirements

USP 34, May 2011].

The Medication Guide on the other hand, is intended to inform patients in appropriate 'lay terms' to facilitate understanding. Consequently, the proposed wording in the Medication Guide deviates slightly from the established USP definition of 'Controlled Room Temperature' by including the lay term 'room temperature' along with the temperature range of the usual and customary working environment of 68°F to 77°F (20°C to 25°C) which is "consistent" with the formal USP Controlled Room Temperature definition.

Therefore, we would ask for FDA's agreement to retain the current wording on the storage conditions in the Medication Guide to meet the specific needs of the intended audience, and not to change it to what appears in the US PI and Container Label.

Also, as indicated in our previous e-mail response on October 24, 2016, the specific language currently proposed in the US PI and Medication Guide reflects our "uniform room temperature storage statements" which have been approved in BI's drug products since 2012 (including Jardiance NDA 204629, Glyxambi NDA 206073, Synjardy NDA 206111, and Jentadueto XR NDA 208026) where room temperature storage is indicated.

Please let me know if you have further questions.

Thanks and best regards, Joachim.

Boehringer Ingelheim

Dr Joachim Troost
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5155 :: (b) (6)
joachim.troost@boehringer-ingelheim.com

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, November 01, 2016 5:23 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Joachim,

I have the following response for you from the Division of Medication Error Prevention and Analysis (DMEPA).

After reviewing your October 24, 2016 email in response to our October 18, 2016 information request, we agree with your proposal to use the phrase "Store at 25°C (77°F)" on the Commercial and Professional Sample versions of your Carton and Container labeling for NDA 208658. Please remember that this statement should be the same for consistency between all of the labeling and labels, including in the Medication Guide.

Let me know if you have any further questions.

Kind regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Monday, October 24, 2016 8:14 AM
To: White, Michael G (CDER)
Cc: heidi.reidies@boehringer-ingelheim.com
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Mike,

In response to the comments and recommendations from DMEPA, please find our response and clarification below. Please let me know if you have any further questions.

Thanks and best regards, Joachim.

Response to FDA for clarification:
The storage statement on the proposed labeling is the result of an internal Audit undertaken by BI to standardize the temperature storage statements across our portfolio of approved drug products. The specific language currently employed in our uniform room temperature storage statements reflects the exact language recommended in FDA's Withdrawn Guidance for Industry: Stability Testing of Drug Substances and Drug Products and has been approved in BI's drug products since 2012 (including Jardiance NDA 204629, Glyxambi NDA 206073, Synjardy NDA 206111, and Jentadueto XR NDA 208026) where room temperature storage is indicated.

Additionally, the storage statements on the label and carton are aligned with Section 16 of our proposed US PI and all labeled storage statements are consistent with USP Controlled Room Temperature as defined.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, October 18, 2016 12:42 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Cc: Reidies,Heidi (MED RA) BIP-US-R
Subject: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Joachim,

We have the following comments and recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) pertaining to your carton and container labels for NDA 208658, Synjardy XR, submitted on February 10, 2016.

Please note that we may have further comments later.

DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Container Label-Commercial

1. **For each of the labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the other container labels to read: "Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.**

B. Carton Labeling and Container Label-Professional Sample

2. **For each of the sample labeling and labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the trade container labels to read: "Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.**

Please resubmit any updated labeling with applicable changes. Let me know if you have any questions and please confirm receipt of this email.

Per instructions from Boehringer Ingelheim, Heidi Reidies, Executive Director, Regulatory Affairs, was copied on this communication.

Kind regards,
-Mike

Michael G. White, PhD

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

/s/

MICHAEL G WHITE
11/09/2016

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING
Date: Tuesday, November 01, 2016 5:57:58 PM

Dear Mike,

Thanks for your reply.

Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, November 01, 2016 5:23 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Joachim,

I have the following response for you from the Division of Medication Error Prevention and Analysis (DMEPA).

After reviewing your October 24, 2016 email in response to our October 18, 2016 information request, we agree with your proposal to use the phrase "Store at 25°C (77°F)" on the Commercial and Professional Sample versions of your Carton and Container labeling for NDA 208658. Please remember that this statement should be the same for consistency between all of the labeling and labels, including in the Medication Guide.

Let me know if you have any further questions.

Kind regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Monday, October 24, 2016 8:14 AM
To: White, Michael G (CDER)
Cc: heidi.reidies@boehringer-ingelheim.com

Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Mike,

In response to the comments and recommendations from DMEPA, please find our response and clarification below. Please let me know if you have any further questions.

Thanks and best regards, Joachim.

Response to FDA for clarification:
The storage statement on the proposed labeling is the result of an internal Audit undertaken by BI to standardize the temperature storage statements across our portfolio of approved drug products. The specific language currently employed in our uniform room temperature storage statements reflects the exact language recommended in FDA's Withdrawn Guidance for Industry: Stability Testing of Drug Substances and Drug Products and has been approved in BI's drug products since 2012 (including Jardiance NDA 204629, Glyxambi NDA 206073, Synjardy NDA 206111, and Jentadueto XR NDA 208026) where room temperature storage is indicated.

Additionally, the storage statements on the label and carton are aligned with Section 16 of our proposed US PI and all labeled storage statements are consistent with USP Controlled Room Temperature as defined.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, October 18, 2016 12:42 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Cc: Reidies,Heidi (MED RA) BIP-US-R
Subject: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Joachim,

We have the following comments and recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) pertaining to your carton and container labels for NDA 208658, Synjardy XR, submitted on February 10, 2016.

Please note that we may have further comments later.

DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Container Label-Commercial

1. **For each of the labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the other container labels to read: "Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-**

30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

B. Carton Labeling and Container Label-Professional Sample

2. **For each of the sample labeling and labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the trade container labels to read: "Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.**

Please resubmit any updated labeling with applicable changes. Let me know if you have any questions and please confirm receipt of this email.

Per instructions from Boehringer Ingelheim, Heidi Reidies, Executive Director, Regulatory Affairs, was copied on this communication.

Kind regards,
-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

/s/

MICHAEL G WHITE
11/01/2016

From: heidi.reidies@boehringer-ingelheim.com
To: White, Michael G (CDER); joachim.troost@boehringer-ingelheim.com
Subject: RE: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING
Date: Tuesday, October 18, 2016 12:49:46 PM

Dear Mike,
I am confirming receipt on behalf of Joachim.
Kind regards,
Heidi

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, October 18, 2016 12:42 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Cc: Reidies,Heidi (MED RA) BIP-US-R
Subject: NDA 208658, Synjardy XR: CARTON & CONTAINER LABELING

Dear Joachim,

We have the following comments and recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) pertaining to your carton and container labels for NDA 208658, Synjardy XR, submitted on February 10, 2016.

Please note that we may have further comments later.

DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Container Label-Commercial

1. **For each of the labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the other container labels to read: "Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.**

B. Carton Labeling and Container Label-Professional Sample

2. **For each of the sample labeling and labels, revise the statement regarding storage, "Store at 25°C (77°F)", for consistency with the trade container labels to read: "Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].". Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.**

Please resubmit any updated labeling with applicable changes. Let me know if you have any questions and please confirm receipt of this email.

Per instructions from Boehringer Ingelheim, Heidi Reidies, Executive Director, Regulatory Affairs, was copied on this communication.

Kind regards,
-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

/s/

MICHAEL G WHITE
10/18/2016

PeRC Meeting Minutes
September 28, 2016

PeRC Members Attending:
John Alexander (Acting PeRC Chairperson)
Meshaun Payne
Jacquline Yancy
Donna Snyder
Hari Sachs
Wiley Chambers
Thomas Smith
Yeruk Mulugeta
Maura O'Leary
Rachel Witten
Gilbert Burkhart
Victor Baum
Adrienne Hornatko-Munoz
Dionna Green
George Greeley
Julia Pinto NON-RESPONSIVE
Karen Davis Bruno
Raquel Tapia
Gerri Baer NON-RESPONSIVE

Agenda

NON-RESPONSIVE

9:45	NDA 208658	Synjardy XR (empagliflozin and metformin hcl) Full Waiver/Partial Waiver/Deferral/Plan (with Agreed iPSP)	DMEP	Michael White	(1)As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

NON-RESPONSIVE

3 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

Synjardy XR (empagliflozin and metformin hcl) Full Waiver/Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Indications: (1) An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
- This product triggers PREA as a new indication, new dosage form and new dosing regimen and has a PDUFA date of December 10, 2016.
- PeRC and the division briefly discussed ongoing pediatric studies of empagliflozin as a single agent that will be used to support labeling for this combination product. The PMR for this NDA application will be for submission of the ongoing pediatric trial.
- *PeRC Recommendations:*
  - The PeRC concurred with the plan for a partial waiver in patients birth to less than 10 years of age (b) (4)

NON-RESPONSIVE

8 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

---

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

/s/

MESHAUN L PAYNE
10/14/2016

From: Lalmansingh, Anika
To: "joachim.troost@boehringer-ingelheim.com"
Subject: NDA 208658 - Information Request, 6/27/2016
Date: Monday, June 27, 2016 4:36:00 PM
Attachments: image001.png

Information Request – CMC only

NDA 208658

Good afternoon Mr. Troost:

We request that you submit a response to the following deficiency by Thursday, July 28, 2016:

1. The batch records for the empagliflozin [redacted] (b) (4) should include the checklist for environmental controls. Revise the master batch records to include this information.

Kindly acknowledge receipt of this email.

Kind Regards.

-Anika

Anika Lalmansingh, PhD
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA

10903 New Hampshire Ave, Bldg #75 Room 4631, Silver Spring, MD 20993-0002
(240) 402-0356 | ✉ anika.lalmansingh@fda.hhs.gov

Anika Lalmansingh

Digitally signed by Anika Lalmansingh
Date: 9/30/2016 10:26:48AM
GUID: 55370d2000cfd6978682b28ff465c2a6

From:	Lalmansingh, Anika
To:	"joachim.troost@boehringer-ingelheim.com"
Cc:	White, Michael G (CDER)
Subject:	NDA 208658 - Information Request, 5/16/2016
Date:	Monday, May 16, 2016 2:16:00 PM
Attachments:	image001.png

Information Request - CMC

NDA 208751

Good afternoon Mr. Troost:

Please submit the following information by June 16, 2016:

1. In accordance with 21 CFR 201.17, the container and carton labels should have a provision for location of the expiration date of the drug product. Revise the labels to show the location of the expiration date.
2. You only submitted carton labels for professional samples. Submit carton labels for the commercial product with the appropriate bar codes.

Please acknowledge receipt of this email.

Kind Regards.

-Anika

Anika Lalmansingh, PhD
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA

10903 New Hampshire Ave, Bldg #75 Room 4631, Silver Spring, MD 20993-0002
(240) 402-0356 | ✉ anika.lalmansingh@fda.hhs.gov

Anika Lalmansingh

Digitally signed by Anika Lalmansingh
Date: 9/30/2016 10:21:10AM
GUID: 55370d2000cfd6978682b28ff465c2a6

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA208658, Synjardy XR: REQUEST FOR INFORMATION
Date: Monday, July 18, 2016 5:16:00 PM

Dear Mike,

receipt confirmed.

Thanks, Joachim

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Monday, July 18, 2016 5:09 PM
To: Troost,Dr.,Joachim (MED RA) BIP-US-R
Subject: NDA208658, Synjardy XR: REQUEST FOR INFORMATION

Dear Joachim,

In reference to your to NDA 208658, Synjardy XR (empagliflozin and metformin hydrochloride extended-release tablets), we have the following request for information from the review team.

The electronic data sets from studies 1276.15 and 1276.28 for concentrations and pharmacokinetic parameters do not have all information (e.g. period, sequence, and treatment) for Agency to confirm the analysis for these pivotal bioequivalence studies. Therefore, provide data sets for the pivotal bioequivalence studies (1276.15 and 1276.28) in separate SAS transport files (.xpt) with following information arranged in columns:

- **the concentrations (including pre-dose concentration) of each analyte with information of treatment, dose, subject number, nominal time, actual time, sequence, period, etc.**
- **the primary pharmacokinetic parameters (including pre-dose concentration) of each analyte with information of subject number, sequence, period, treatment, dose, etc.**

Please provide this information as soon as possible or by the close of business Monday, **August 1, 2016**.

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

Kind regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

/s/

MICHAEL G WHITE
07/18/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208658

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Joachim Troost, MD
Sr. Associate Director, Regulatory Affairs

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated February 10, 2016, received February 10, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Empagliflozin and Metformin HCl Extended-Release Tablets, 5 mg/1000 mg, 10 mg/1000 mg, 12.5 mg/1000 mg, and 25 mg/1000 mg.

We also refer to your March 2, 2016, correspondence, received March 2, 2016, requesting review of your proposed proprietary name, Synjardy XR.

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

If any of the proposed product characteristics as stated in your March 2, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-3981. For any other information regarding this application, contact Michael White, Regulatory Project Manager in the Office of New Drugs, at 240-402-6149.

Sincerely,

{See appended electronic signature page}

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

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

/s/

TODD D BRIDGES
05/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208658

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated and received February 10, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for empagliflozin and metformin hydrochloride extended-release tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **December 10, 2016**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 12, 2016.

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.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage

you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

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

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

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

PROMOTIONAL MATERIAL

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

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

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

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
04/20/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208658

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

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

Name of Drug Product: Empagliflozin and metformin hydrochloride extended-release tablets

Date of Application: February 10, 2016

Date of Receipt: February 10, 2016

Our Reference Number: NDA 208658

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 April 10, 2016, 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

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 (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Michael G. White, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MICHAEL G WHITE
02/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111919

**MEETING REQUEST-
WRITTEN RESPONSES**

Boehringer Ingelheim Pharmaceuticals Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

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

We also refer to your submission dated May 18, 2015, containing a Type B meeting request. The purpose of this request is to seek FDA concurrence on the proposed format and content of a complete new drug application for empagliflozin and metformin hydrochloride extended-release FDC tablets for patients with type 2 diabetes.

Further reference is made to our Meeting Granted letter dated May 22, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 18, 2015, background package.

If you have any questions, call Michael White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Other (Pre-NDA)
Application Number:	IND 111919
Product Name:	empagliflozin and metformin hydrochloride extended-release fixed dose combination tablets
Indication:	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride (b) (4) is appropriate
Sponsor Name:	Boehringer Ingelheim Pharmaceuticals Inc.
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) is developing various strengths of fixed-dose combination (FDC) tablets for empagliflozin plus extended release (ER) metformin hydrochloride (HCl) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes where treatment with empagliflozin and metformin is appropriate.

BI submitted a combined Pre-IND meeting request for PIND 111919 (empagliflozin/metformin hydrochloride ER FDC tablets) and PIND 111970 (linagliptin/metformin hydrochloride ER FDC) on May 25, 2011, with preliminary comments provided on October 11, 2011. After a period of inactivity resulting in administrative withdrawal of PIND 111919, it was reinstated on January 28, 2013, at the request of the sponsor.

BI opened IND 111919 for empagliflozin/metformin hydrochloride ER FDC on September 18, 2013. On December 23, 2013, BI submitted a request for a Type C guidance meeting in order to obtain FDA input related to the proposed Phase 1 clinical development program, CMC development and stability requirements, and tablet differentiation strategy for this drug product. Written responses were provided by the Agency on March 10, 2014.

BI states that "agreement was reached in these meetings on a 'Phase 1 only' program in support of registration which compares co-administration of single entity tablets empagliflozin and metformin HCl to the 'to be marketed' FDC." BI goes on to state that "Phase 1 studies were performed with FDC tablet strength formulation of 25 mg empagliflozin/1000 mg ER metformin hydrochloride and 10 mg empagliflozin/1000 mg ER metformin hydrochloride." BI states its intention to request biowaivers for additional FDC strengths.

BI states its opinion that this approach will allow bridging of safety and efficacy data for the proposed empagliflozin/metformin hydrochloride ER FDC to existing studies with Jardiance (empagliflozin, NDA 204629) and Synjardy (empagliflozin/metformin HCl immediate release FDC tablets, NDA206111), for which BI is also the NDA holder. BI also states this approach will allow bridging to the safety and efficacy data for Glumetza (ER metformin tablets, NDA 021748), for which BI has obtained a right of reference and full access to all information.

BI goes on to state that it has "Completed the Phase 1 pivotal studies which have demonstrated bioequivalence," and it is planning to submit results, along with cross references to the full safety and efficacy data from aforementioned approved NDAs, in a new NDA for empagliflozin/metformin hydrochloride ER FDC tablets be filed under the 505(b)(1) pathway.

BI notes that this planned NDA is "Comparable to the upcoming linagliptin/metformin HCl extended release FDC NDA, targeted for submission in July 2015." BI thus proposes that the NDA for empagliflozin/metformin hydrochloride ER FDC follow a similar pathway to registration that was discussed in the pre-NDA meeting written responses for linagliptin/metformin hydrochloride ER FDC (IND 111970) sent by the agency on January 6, 2015, as well as additional comments regarding the 4-month safety update sent by the Agency via email on March, 4, 2015.

On May 18, 2015, BI submitted a request for a written-response, pre-NDA meeting in order to obtain FDA comment on the proposed format and content of a complete new drug application for empagliflozin/metformin hydrochloride ER FDC tablets.

2.0 QUESTIONS AND RESPONSES

2.1. Chemistry, Manufacturing and Controls

Question 1: 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 to Question 1:*** ***We note that your NDA will be a 505(b)(1) application. Therefore, we agree to the proposed content and application format of the CMC information on the drug product in the new NDA, and to the cross-reference to the CMC information on the drug substances empagliflozin and metformin hydrochloride (NDA 204629, NDA 206111, and DMF*** (b) (4).

2.2. Nonclinical Pharmacology

Question 2: Does the Division concur with [the sponsor's] approach [to cross-referencing non-clinical information in previously approved products, including supplying a Nonclincial Overview but not including Nonclinical Written and Tabulated Summaries]?

> ***FDA Response to Question 2:*** **Yes, your nonclinical approach for the planned NDA is acceptable.**

2.3. Quality/Biopharmaceutics

Question 3: Does the Agency concur with [the sponsor's] approach [to bioequivalence studies including requesting a biowaiver for the additional strengths]?

> ***FDA Response to Question 3:*** **Since you conducted the pivotal bioequivalence studies with the 25 mg empagliflozin/1000 mg extended-release metformin hydrochloride and 10 mg empagliflozin/1000 mg extended-release metformin hydrochloride strengths, we concur with your plan, that you will submit a biowaiver request for the other additional strengths, as we advised you in our March 10, 2014, letter.**

2.4. Clinical

Question 4: Does the Division concur with this cross-reference strategy [for existing safety and efficacy data from the clinical studies of previously approved products]?

> ***FDA Response to Question 4:*** **Your plan to cross-reference the Jardiance NDA and Glumetza NDA for the existing safety and efficacy data is reasonable assuming that the results of the bioequivalence studies support a bridge to your fixed combination drug product.**

Question 5: Does the Division concur with [the sponsor's] approach [to the inclusion of new clinical data, including submitting a Clinical Overview, but not submitting a Clinical Summary nor a Summary of Safety or Integrated Summary of Effectiveness]?

> ***FDA Response to Question 5:*** **We agree that clinical summaries are not necessary as support for the proposed NDA will come from phase 1 studies only.**

Question 6: Does the Division concur with [the sponsor's] approach [to the inclusion of case report tabulation datasets, case report forms, safety narratives, and bioavailability studies]?

> ***FDA Response to Question 6:*** **Your proposed approach of submitting datasets, case report forms and narratives for the two pivotal phase 1 studies is acceptable. Your proposal to only submit complete study reports for the relative bioavailability studies is reasonable, provided that datasets, case report forms, and narratives will be available if requested. It is our understanding that SAS transport files for PK concentrations and PK derived parameters will be included in the submission. We acknowledge that you will provide case report forms and narratives for all serious adverse events and for all discontinuations due to an adverse event for all of the studies.**

2.5. 4 Month Safety update

Question 7: Does the Division concur with the proposed content and format of the 4MSU?

FDA Response to Question 7: **In addition to submitting a summary report for post-marketing data and information from the medical literature for the pending empagliflozin/metformin IR NDA, you should also submit a similar summary report with information from the empagliflozin NDA.**

2.6. OSI / Regulatory

Question 8: Does the Division concur with [the sponsor's] approach [to the Office of Scientific Investigations (OSI) requests]?

FDA Response to Question 8: **We concur. OSI's routine inspection request is not needed.**

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and ***PLLR Requirements for Prescribing Information*** websites including:

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

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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
07/16/2015