CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212614Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 24, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 212614
Product Name and Strength:	Trijardy XR (empagliflozin, linagliptin, and metformin extended release tablet), 25 mg/5 mg/1,000 mg, 12.5 mg/2.5 mg/1,000 mg, 10 mg/5 mg/1,000 mg, 5 mg/2.5 mg/1,000 mg
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
OSE RCM #:	2019-699-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling for Trijardy XR on January 17, 2020. We reviewed the revised container labels and carton labeling for Trijardy XR (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions were made to align with changes that were made to the prescribing information (i.e. revised storage information, dosage statement, and placement of dosage form within the established name).[a]

2 CONCLUSION

The revised carton and container labels are acceptable from a medication error perspective and we have no additional recommendations at this time.

[a] Cover Letter: Amendment to Pending NDA 212614 (empagliflozin, linagliptin, and metformin extended release). Ridgebury (CT): Boehringer Ingelheim; 2020 Jan 17. Available from: \\cdsesub1\evsprod\nda212614\0023\m1\us\cover-letter.pdf.

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ARIANE O CONRAD
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HINA S MEHTA
01/24/2020 10:37:25 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 30, 2019
To:	Michael G. White, PhD Senior Regulatory Project Manager **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Reviewer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 212614
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On March 27, 2019, Boehringer Ingelheim Pharmaceuticals, Inc., submitted for the Agency's review a New Drug Application (NDA) 212614 for TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release) tablets, for oral use. This NDA is proposing an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on April 8, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release) MG received on March 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 16, 2019.
- Draft TRIJARDY XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release) Prescribing Information (PI) received on March 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 16, 2019.
- Approved SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release) comparator labeling dated October 26, 2018.
- Approved GLYXAMBI (empagliflozin and linagliptin) comparator labeling dated July 3, 2019.
- Approved GLUMETZA (metformin hydrochloride) comparator labeling dated November 7, 2018.
- Approved JARDIANCE (empagliflozin) comparator labeling dated October 26, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
12/30/2019 01:56:55 PM

LASHAWN M GRIFFITHS
12/30/2019 02:07:33 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 23, 2019

To: Michael White, Regulatory Project Manager, Division of Metabolism and Endocrinology Products (DMEP)

LaiMing Lee, Associate Director for Labeling, DMEP

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRIJARDY™ XR (empagliflozin, linagliptin, and metformin hydrochloride extended-release) tablets, for oral use

NDA: 212614

In response to DMEP's consult request dated April 8, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Trijardy XR.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP on December 20th, 2019 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 22, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Savani at (240) 402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 4, 2019

TO: Lisa Yanoff, MD
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDSI
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of studies 136
ed at (b) (4)

I did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

Study 1361-0003 (NDA 212614, Metformin analysis only)
"Bioequivalence of a fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration

in healthy male and female subjects (an open-label, randomized, single-dose, two-period, two-sequence crossover study)"
Sample Analysis Period: 11/15/2017 - 11/29/2017

Study 1361-0011 (NDA 212614, Metformin analysis only)
"Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomized, single-dose, two-period, two-sequence crossover study)"
Sample Analysis Period: 11/09/2018 - 11/26/2018

2.1. Studies not yet associated with an application

[redacted] (b) (4)

3. Scope of Inspection

OSIS scientist Kara A. S[redacted]rtion at [redacted] (b) (4) fro[redacted] (b) (4)

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff. In addition to stu[redacted]of 4, study [redacted] (b) (4) (b) (4) was chosen as part of this surveillance inspection.

4. Inspectional Findings

At the conclusion of the inspection, I did not observe objectionable conditions. I did not issue Form FDA 483 to [redacted] (b) (4) (b) (4), and there were no discussion items conveyed to the firm during the closing meeting.

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable.

Studies using similar methods conducted between the previous inspection ([redacted] (b) (4)) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI- [redacted] (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Scheibner
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov

Draft: KAS 12/02/2019
Edit: MFS 12/02/2019; JAK 12/04/2019

ECMS:http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a01509
OSIS File #: [redacted] (b) (4)

FACTS: [redacted] (b) (4)

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/s/

KARA A SCHEIBNER
12/04/2019 01:15:59 PM

MICHAEL F SKELLY
12/04/2019 01:18:05 PM

JOHN A KADAVIL
12/04/2019 01:19:54 PM

Clinical Inspection Summary

Date	12/4/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Anthony Orencia, M.D., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Frank Pucino, Pharm. D., M.P.H., Clinical Reviewer Patrick Archdeacon, M.D., M.Phil., Clinical Team Leader Michael G. White, Ph.D., Senior Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	212614
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Drug	Empagliflozin/linagliptin/metformin hydrochloride
NME	No
Therapeutic Classification	Antidiabetic Agents, Non-Insulin
Proposed Indication	Treatment of type 2 diabetes mellitus
Consultation Request Date	5/7/2019
Summary Goal Date	12/10/2019
Action Goal Date	1/27/2020
PDUFA Date	1/27/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of three domestic and three foreign clinical sites. Furthermore, there was a previous for-cause inspection of a domestic site that was involved with one of the studies under investigation.

The inspection of two clinical investigators listed below (including the previous for-cause inspection of a domestic site) revealed regulatory deficiencies which are unlikely to have a significant impact on overall results. The inspection of the remaining clinical investigators revealed no regulatory violations. Based on the inspections, the study data generated are considered acceptable and may be used in support of this NDA.

II. BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted an original new drug application for empagliflozin, linagliptin, and metformin hydrochloride extended-release tablets to be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (b) (4) .

Jardiance® (empagliflozin), Tradjenta® (linagliptin), Jentadueto® (linagliptin/metformin hydrochloride), Synjardy® (empagliflozin/metformin hydrochloride), and Glyxambi® (empagliflozin/linagliptin) have all been previously approved.

Inspections were requested for two studies:

- Study 1275.9: "A phase III, randomized, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy."

- Study 1275.10: "A phase III, randomized, double-blind, parallel group study to evaluate the efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combination with empagliflozin 10 mg or 25 mg for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycemic control after 16 weeks of treatment with empagliflozin 10 mg or 25 mg on metformin background therapy"

Study 1275.9
The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin 25 mg (empa 25) and empagliflozin 10 mg (empa 10) compared with placebo, each administered as add-on therapy to linagliptin 5 mg (lina 5) and metformin, over 24 weeks in subjects with type 2 diabetes (T2DM), who had met the HbA1c inclusion criterion (HbA1c $\geq$7% and $\leq$10.5%) after 16 weeks of open-label (OL) treatment with lina 5 OL and metformin background treatment. Subjects had to be treated with metformin at an unchanged dose for at least 12 weeks before start of open-label treatment.

After 16 weeks (Visit 4) in the open-label treatment period, subjects were to enter a 1 week open-label placebo add-on period in order to complete further eligibility evaluations before being randomized to the 24-week treatment period at a ratio of 1:1:1 to empa 25/lina 5 OR empa 10/lina 5 OR lina 5.

The primary endpoint was the change from baseline in HbA1c (%) after 24 weeks of double-blind trial treatment. Baseline was defined as the last value before the first intake of any randomized, double-blind trial treatment.

This was a multinational trial in 90 sites in 10 countries. The study began March 1, 2013 and completed March 23, 2015. There were 1134 subjects screened, 606 subjects that entered the open-treatment arm, 333 subjects that were randomized, and 314 subjects that completed the 24-week double-blind treatment.

Study 1275.10
The objective of this trial was to investigate the efficacy, safety, and tolerability of linagliptin 5 mg (lina 5) compared with placebo, each administered as add-on therapy to empagliflozin 25 mg (empa 25) or empagliflozin 10 mg (empa 10) and metformin, over 24 weeks in subjects with type 2 diabetes (T2DM), who had met the HbA1c inclusion criterion (HbA1c ≥7% and ≤10.5%) after 16 weeks of open-label (OL) treatment with empa 25 OL or empa 10 OL and metformin background treatment.

Subjects were randomized to treatment at two different times during the trial. At Visit 2, the subject was either randomized to open-label treatment with empa 25 OL or empa 10 OL in a 1:1 ratio. After a 16-week open-label treatment period, the subjects received placebo in addition to empa 25 OL or empa 10 OL for 1 week while awaiting laboratory results from Visit 4. At Visit 5, subjects who remained eligible and had met the HbA1c inclusion criteria with empa 25 OL treatment (HbA1c ≥7.0% and ≤10.5% at Visit 4) were randomized at a 1:1 ratio to double-blind treatment with lina 5 or placebo, both as add-on to empa 25 and metformin treatment. This group was referred to as study population A. The subjects randomized to lina 5 received empa 25/lina 5, while subjects randomized to placebo received placebo and empa 25 as two separate tablets. Subjects who met the HbA1c inclusion criteria with empa 10 OL treatment were randomized at a 1:1 ratio to double-blind treatment with lina 5 or placebo, both as add-on to empa 10 and metformin treatment. This group was referred to as study population B. The subjects randomized to lina 5 received empa 10/lina 5; subjects randomized to placebo received placebo and empa 10 as 2 separate tablets.

Statistical analyses for the two trial populations were to be evaluated separately. All double-blind trial treatments were administered orally once daily for 24 weeks. As per trial design, subjects well-controlled on empa 25 or empa 10 open-label treatment had to be excluded from the trial at the end of the 16-week empagliflozin open-label period.

The primary endpoint was the change from baseline in HbA1c [%] after 24 weeks of double-blind trial treatment. Baseline was defined as the last value before first intake of any randomized, double-blind trial treatment.

This was a multinational trial in 114 sites in 10 countries. There were 1324 subjects enrolled, 709 subjects entered the empa OL, and 482 subjects were randomized to double-blind treatment; 436 subjects completed the study. The study began February 13, 2013 and completed March 30, 2015.

Site 1019 (Martinez/US) and Site 54012 (Pelegrina/Argentina) were closed for cause due to serious non-compliance.

III. RESULTS (by Site):

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. **Eddie Armas, M.D.**
   Well Pharma Medical Research
   7000 Southwest 62nd Avenue, Suite 100
   Miami, FL 33143

   Site: 1011 **Study:** 1275.10

Dates of inspection: August 19 – 23, 2019

There were 34 subjects screened at the site. A total of 18 subjects were enrolled into the initial 16-week open-label portion of the trial; subsequently, 7 subjects enrolled into study Part A and 6 subjects enrolled into study Part B; 12 subjects completed the study. There were 12 subject records reviewed.

There are two separate entities within the study site office, ALCA Medical Center and Well Pharma Medical Research. Both are owned by Dr. Armas. ALCA is the private medical practice of Dr. Armas. The practice was started in 2005 and is independent of the research functions of Well Pharma. Dr. Armas also opened a small ALCA satellite office in another part of town. This office is run by Maria Valdez, MD who is sometimes involved with the studies at Well Pharma. Dr. Armas recruited subjects for various studies from both practices. He also gets referrals from other doctors in the area.

Well Pharma was started by Dr. Armas (b) (6) Dr. Armas as the sole owner. Well Pharma is the location where the study took place.

(b) (4) was the IRB of record.

The study records and subject files were well organized. The source documents were paper with a set of paper worksheets that were used to collect visit data. This data was then transcribed into the electronic case report form (eCRF).

All subjects met initial eligibility qualifications, and the additional qualifications for randomization into the study at Visit 5. There was one serious adverse event that was reported to the sponsor and IRB after the 24-hour timeframe. There was a corrective action plan and retraining.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Josefa L. Binker, M.D.
Binker Medical Center
70 NW 8th Street
Homestead, FL 33030

Study 1275.9 was conducted at Community Research Foundation, Inc., 6700 SW 21st Street, Miami, FL 33155. That location has closed.

Site: 1004 **Study:** 1275.9

Dates of inspection: July 16 – 25, 2019 (two separate applications were inspected).

There were 29 subjects screened and 12 subjects enrolled into the open-label phase; 11 subjects were randomized; 11 subjects completed the study. There were 12 subject records reviewed.

In 2006, Dr. Binker opened Binker Medical Center with her husband, Dr. Rodolfo Binker. Dr. Binker devotes 50-80% of her time to research versus her clinical practice. Subjects were patients from Dr. Binker's private practice.

(b) (4) was the IRB of record.

The study source records were organized and available. Data was transcribed into the study eCRF. Source was compared to the sponsor data line listings. There were no discrepancies.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for not following the protocol. Specifically, Subject, # (b) (6) was enrolled without meeting inclusion criteria #3, "HbA1c ≥ 8.0% and ≤ 10.5% at Visit 1 for entering the 16-week treatment period." The subject's HbA1c value was 7.7% at Visit 1. The subject was dispensed open-label linagliptin on (b) (6). The subject was prematurely terminated at Visit 3 on (b) (6) when the site realized that the subject did not meet eligibility at the screening visit. Of note, the inclusion requirement at Visit 4 for HbA1c was ≥ 7.0% and

≤ 10.5%. Dr. Binker stated that due to the two different inclusion requirements for HbA1c at Visit 1 and Visit 4, the site got confused.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

3. Pedro R. Fabian Calella, M.D.
Centro Integral de Prevención y Atención en Diabetes
Cristobal Colon 776
Godoy Cruz, Mendoza
M5501ARP
Argentina

Site: 54003 **Study:** 1275.10

Dates of inspection: September 23 – 26, 2019

There were 32 subjects screened at the site. A total of 20 subjects were enrolled into the initial 16-week open-label portion of the trial; subsequently, 10 subjects enrolled into study Part A and 6 subjects enrolled into study Part B; 16 subjects completed the study. There were 14 subject records reviewed.

A translator was present throughout the inspection. She also generated several typed partial and full-page direct translations of study documents as requested by the FDA inspector.

Dr. Calella originally initiated the study at his practice located at 25 De Mayo 1744 Mendoza, Argentina (M5500EV) until his practice moved in January 2014. All subjects were recruited from Dr. Calella's medical practice. The site was a non-IND site.

The [redacted] (b) (4) was the ethics committee of record.

Source records were organized and available. All source records were maintained in paper and electronic form. Clinical histories/ visit notes were electronically transcribed by the clinical investigator/subinvestigator during the visit. Delegated study personnel were responsible for entering source data into the eCRFs.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. **Patricia M. Castaño, M.D.**
   Instituto Médico Especializado
   Departamento de Nutrición, Metabolismo y Diabetología
   Capital Federal
   Buenos Aires Hidalgo 568
   C1405BCH
   Argentina

   Site: 54013 **Study:** 1275.10

Dates of inspection: October 21 – 24, 2019

There were 54 subjects screened at the site (representing 51 unique patients; 3 subjects were rescreened). A total of 30 subjects were enrolled into the initial 16-week open-label portion of the trial; subsequently, 12 subjects enrolled into study Part A and 6 subjects enrolled into study Part B; 16 subjects completed the study. There were 18 subject records reviewed.

A translator was present throughout the inspection.

The Instituto Medico Especializado Departamento de Nutricion, Metabolismo y Diabetologia was a private outpatient institution dedicated to patient care and clinical research. In January 2019, the facility changed ownership and the focus has shifted from clinical research activities to that of an outpatient clinic. Currently, there are still clinical research activities as Dr. Castaño and one sub-investigator still conduct clinical trials at this institution, with 3 trials currently on-going. Dr. Castaño has been involved in clinical research for the past 15 years. Dr. Castaño also serves as a nutrition and diabetes specialist at a local hospital and has her own private clinic. The site was a non-IND site.

(b) (4) was the ethics committee of record.

Study records were orderly and available for inspection. Separate and dedicated paper files were maintained for each subject. No electronic medical records were used at the time the trial was conducted. There were dedicated Trial Master File binders that included general and regulatory records.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

5. Baudilio J. Cusco-Prieto, M.D.
Clinical Therapeutics Corporation
P.O. Box 144192
470 Biltmore Way, Suite 104
Coral Gables, FL 33134-5788

The firm was previously located at Suite 102 (the address in the application). After the study concluded, the Corporation down-sized to a smaller suite, Suite 104, at the same address.

Site: 1010 **Study:** 1275.9

Dates of inspection: July 9 – 12, 2019

There were 62 subjects screened, and 58 subjects enrolled into the open-label phase; 29 subjects were randomized; 20 subjects completed the study. There were 20 subject records reviewed.

Dr. Cusco is the Medical Director of Clinical Therapeutics Corporation as well as an investigator and a sub-investigator. He has had a private medical practice since 1975. Subjects were recruited from the private practice. There was no advertisement used.

(b) (4) was the IRB of record.

The source documents consisted of paper records which were well organized, in good condition, legible and complete. The eCRFs were transcribed by the study coordinators from information contained in the subject source documents.

The inspection found that subjects met the study eligibility criteria and were enrolled appropriately. The protocol blinding and randomization procedures were followed. The study blind was not broken throughout the course of the study at this site.

Source records were compared to the sponsor data line listings. There were no discrepancies.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

6. Manel Terns Riera, M.D.
EAP Vic
Passatge Del Pla Del Remei 10-12
Vic 8500 Barcelona
Spain

Site: 34006 **Study**: 1275.9

Dates of inspection: July 8 – 11, 2019

There were 19 subjects screened and 11 subjects randomized (could not confirm how many were in the open-label phase); 11 subjects completed the study. There were 19 subject records reviewed.

A translator was present throughout the inspection.

EAP Vic is a medical center that serves approximately half of the residents of Vic, Spain (25,000 people). Two days are reserved for study activity and normal medical practice activities occur the other days of the week. All subjects for this study were recruited from the patient population at EAP Vic.

The reference independent ethics committee of record for this and all studies in Spain was (b) (4). In addition to the reference ethics committee, a local ethics committee was provided all information about the study and was able to offer comments to the reference ethics committee when desired. The local ethics committee was (b) (4).

Subject records were in both electronic format and paper format. Study staff entered source information into the eCRF. Source records were compared to the sponsor data line listings. There were no discrepancies noted.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

7. Gilbert J. Martinez, M.D.
Catalina Research Institute
14726 Ramona Ave, Ste. 100 and 110
Chino, CA 91710

Site: 1019 **Study**: 1275.9

Dates of inspection: November 03 – 25, 2014 (included two separate applications)

This inspection of Dr. Martinez was conducted for cause in response to a report from Boehringer Ingelheim, on July 24, 2014. The sponsor reported closure of Dr. Martinez's site due to noncompliance. No sensitivity analysis was performed excluding data from this site. The sponsor has included all subjects in all analyses.

There were 51 subjects screened; 18 subjects enrolled into the open-label phase of the study; 12 subjects were randomized. No subjects completed the study; four were lost to follow up, one was excluded, and one withdrew consent. The other six subjects were discontinued when the sponsor terminated the site. There were 51 subject records reviewed.

Dr. Martinez was hired by Mr. Jose D. Calleros, CEO of Catalina Research Institute (CRI), to conduct clinical research. Dr. Martinez and all employees of CRI report to him. Subjects were recruited through community health fairs and word of mouth. Most of the subjects who were screened were former patients of (b) (6). (b) (6) closed his practice and referred his patients to CRI.

(b) (4) was the IRB of record.

The source documents were arranged in case folders. There were no progress notes to document that Dr. Martinez met with the subjects. Visit worksheets described the procedures that were conducted for the visits. Dr. Martinez's signature was present on source documents such as test results and visit worksheets. He made determinations about the clinical significance of abnormal EKGs and out-of-range laboratory results. The sponsor cited lack of investigator involvement as a reason for termination of the site and there was limited evidence in the source documentation to support that the investigator was actively involved in the trial. The monitor reports showed that Dr. Martinez was instructed to add notes to the subject records. Several notes were completed long after the visits.

The monitor reported that adverse events were missing for several subjects. Dr. Martinez entered the missing adverse events into the eCRF before the sponsor terminated the site. Dr. Martinez assessed the severity of each adverse event and documented its relationship to the test article in the source documents.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to conduct the investigation in accordance with the signed statement of the investigator and the investigational plan. Specifically, Protocol 1275.10 excludes subjects who have uncontrolled hyperglycemia with a fasting blood glucose level >270

mg/dl during the open label period (from Visit 2 to Visit 4) and confirmed by a second measurement (not on the same day and done either at the central or local laboratory). Subject (b) (6) had a fasting blood glucose level of 351 mg/dL at Visit 2 and was not contacted to return to the site for a retest. Subject remained in the study until Visit 3 (approximately 7 weeks later) where hyperglycemia was confirmed by repeated fasting blood glucose. The subject was then withdrawn from the study.

Dr. Martinez failed to have medical records to support patient eligibility for 37 of 51 subjects screened, and 16 out of 18 subjects enrolled. Dr. Martinez screened approximately 45 subjects who were patients of (b) (6). Dr. Martinez used patient questionnaires filled out by (b) (6) as medical records to satisfy the inclusion criteria of T2DM diagnosis and metformin usage. Dr. Martinez was warned by the sponsor's monitor during the trial that he was required to have medical records on file prior to consent. This issue was first identified on 10/29/13 during a monitor visit. Dr. Martinez continued to screen subjects without medical records to confirm eligibility despite the monitor informing him it was required. When terminating the site, the sponsor cited lack of medical records to support subject eligibility; 2 subjects (Subject (b) (6) and Subject (b) (6)) had fasting blood glucose over 270 mg/dL and were not contacted for repeat testing. There no medical records for 11 of the 12 subjects who were randomized.

The OSI Compliance Enforcement Branch Significant Action Meeting was held February 10, 2015. Although regulatory violations were noted as described above, it was determined that they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Anthony Orencia, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm./ NDA 212614
DMEP/Acting Division Director/ Lisa Yanoff
DMEP /Acting Deputy Director/William Chong
DMEP/Team Lead/Patrick Archdeacon
DMEP/Clinical Reviewer/ Frank Pucino
DMEP /Regulatory Project Manager/Michael G. White
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Acting Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

CYNTHIA F KLEPPINGER
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 26, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 212614
Product Name and Strength:	Trijardy XR (empagliflozin, linagliptin, and metformin extended release) tablet, 25 mg/5 mg/1,000 mg, 12.5 mg/2.5 mg/1,000 mg, 10 mg/5 mg/1,000 mg, 5 mg/2.5 mg/1,000 mg
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
OSE RCM #:	2019-699-1
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling for Trijardy XR on November 22, 2019. We reviewed the revised container labels and carton labeling for Trijardy XR (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note our recommendation of adding a comma to all numbers greater than or equal to 1,000 in our previous review. BI responded with their preference to display 1000 without a comma to avoid potential confusion for the reader when both a comma and decimal point are included within the same strength statement. In addition, the proposal to display 1000 without a comma for all dosage strengths provides for consistency across dose presentations. We note

[a] Conrad A. Label and Labeling Review for Trijardy XR (NDA 212614). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Nov 5. RCM No.: 2019-699.

the exclusion of the comma would not likely lead to confusion as there are three parts to the strength presentation as the product contains three separate components.

Thus, the revised carton and container labels are acceptable from a medication error perspective. We have no additional recommendations at this time.

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11/26/2019 04:57:33 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: Nov 15, 2019

TO: Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance

SUBJECT: Routine inspection of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach An der Riss, Germany

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of studies 1361.3 and 1361-0011(NDA 212614) conducted at Boehringer Ingelheim Pharma GmbH & Co. KG (BI), Biberach An der Riss, Germany.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2 Inspected Studies:

NDA 212614

Study Number: 1361.3

Study Title: **"Bioequivalence of a fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomized, single-dose, two-period, two-sequence crossover study)"**

Dates of conduct: 09/04/2017 – 11/13/2017

Study Number: 1361-0011
Study Title: **"Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open label, randomized, single-dose, two-period, two-sequence crossover study)"**

Dates of conduct: 09/03/2018 – 11/05/2018

Clinical site: Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach An der Riss, Germany

ORA investigator Richard W. Berning inspected BI, Biberach An der Riss, Germany from August 12-15, 2019.

The inspection included a thorough examination of study records (electronic data), subject records, informed consent process, protocol compliance, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

At the conclusion of the inspection, investigator Berning did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. No discussion items were brought to the site's attention.

4. Conclusion:

After reviewing the inspectional report, I conclude the data from studies 1361.3 and 1361-0011 (NDA 212614) are reliable.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (August 2016) and the end of the current surveillance interval should be considered reliable without an inspection.

Xiaohan Cai, Ph.D.
Senior Staff Fellow

Final Classification:

NAI- Boehringer Ingelheim Pharma GmbH & Co. KG
Biberach An der Riss, Germany
FEI#: 3002806518

cc:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Cai
ORA/OMPTO/OBIMO/FDAInternational BIMO@fda.hhs.gov

Draft: XHC 10/28/2019; 11/14/19
Edit: YMC 10/28/19; 11/12/19;JC 11/12/19

ECMS: Cabinets/CDER_OTS/Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Boehringer Ingelheim Pharma GmbH & Co., (Birkendorfer Straße 65), Germany

OSIS File #: (b) (4)

FACTS: 11930360

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 5, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 212614
Product Name and Strength:	Trijardy XR (empagliflozin, linagliptin, and metformin extended release) tablet, 25 mg/5 mg/1,000 mg, 12.5 mg/2.5 mg/1,000 mg, 10 mg/5 mg/1,000 mg, 5 mg/2.5 mg/1,000 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
FDA Received Date:	March 27, 2019
OSE RCM #:	2019-699
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Trijardy XR (empagliflozin, linagliptin, and metformin extended release), submitted under NDA 212614 on March 27, 2019, to determine if they are acceptable from a medication error perspective.

Boehringer Ingelheim (BI) currently markets Tradjenta (linagliptin, NDA 201280 approved May 2, 2011) and Synjardy XR (empagliflozin and metformin extended-release, NDA 208658 approved December 9, 2016) which are both indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes. The Applicant proposes to introduce a product that contains all three active ingredients (linagliptin, empagliflozin, and metformin extended-release) under the proprietary name Trijardy XR[a] as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) .

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), medication guide, container labels, and professional sample labels and labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We noted

[a] Conrad A. Proprietary Name Review for Trijardy XR (NDA 212614). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US): 2019 Jun 13. RCM No.: 2019-30480044.

areas that could be clarified within the proposed labels and labeling, and we provide recommendations in Section 4.1 and Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Trijardy XR are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. We recommend listing numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" (e.g., change 1000 to 1,000 and 2000 to 2,000).
2. Under Section 2.1 Recommended Dosage, we recommend revising the sub-bullets under the statement "TRADENAME XR should be taken orally once daily with a meal in the morning." to include the product name with each tablet strength for improved clarity as follows:
    - "TRADENAME XR 10 mg/5 mg/1000 mg or TRADENAME XR 25 mg/5 mg/1000 mg should be taken as one single tablet.
    - TRADENAME XR 5 mg/2.5 mg/1000 mg or TRADENAME XR 12.5 mg/2.5 mg/1000 mg should be taken as two tablets (b) (4)."

4.2 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. (BI)

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

A. Container Labels-Trade

1. To ensure consistency with the Prescribing Information, revise the statements "(b) (4)" and "(b) (4)." to read "Dosage: See Prescribing Information."
2. We recommend revising the statement "(b) (4)" to read "Dispense with accompanying Medication Guide" to include how the Medication Guide will be provided per 21 CFR 208.24(d).
3. We recommend listing numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" (e.g., change 1000 to 1,000 and 2000 to 2,000).
4. We note that the location of the lot number and expiration date are not indicated. A lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Therefore, we recommend that you submit revised labels with the locations of the lot number and expiration date clearly noted for Agency review.

5. In addition, we note that the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

6. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

   The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

B. Container Label and Carton Labeling-Professional Sample

1. See A.1 through A5.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trijardy XR received on March 27, 2019 from Boehringer Ingelheim Pharmaceuticals, Inc. (BI).

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Trijardy XR</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>empagliflozin, linagliptin and metformin hydrochloride extended-release</td></tr>
<tr><td>Indication</td><td>an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>tablet</td></tr>
<tr><td>Strength</td><td>5 mg/2.5 mg/1,000 mg, 10 mg/5 mg/1,000 mg, 12.5 mg/2.5 mg/1,000 mg, and 25 mg/5 mg/1,000 mg</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th>mg empagliflozin/mg linagliptin/mg metformin hydrochloride extended release</th><th>Posology</th></tr>
<tr><td>25/5/1000</td><td>1 tablet, once daily</td></tr>
<tr><td>12.5/2.5/1000</td><td>2 tablets, once daily</td></tr>
<tr><td>10/5/1000</td><td>1 tablet, once daily</td></tr>
<tr><td>5/2.5/1000</td><td>2 tablets, once daily</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>bottles of 30, 60, 90, or 180 tablets</td></tr>
<tr><td>Storage</td><td>Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]</td></tr>
<tr><td>Container Closure</td><td>HDPE bottles with a (b) (4) closure</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 12, 2019, we searched for previous DMEPA reviews relevant to this current review using the term “NDA 212614”. Our search identified 0 previous reviews.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Trijardy XR labels and labeling submitted by Boehringer Ingelheim Pharmaceuticals, Inc. (BI).

- Container Labels received on March 27, 2019
- Professional Sample Container Labels received on March 27, 2019
- Professional Sample Carton Labeling received on March 27, 2019
- Prescribing Information and Medication Guide received on March 27, 2019
    - o \\cdsesub1\evsprod\nda212614\0000\m1\us\proposed.doc

C.2 Label and Labeling Images

Trade

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 9, 2019

TO: Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Stanley Au, Pharm.D.
Deputy Director (Acting)
DNDBE, OSIS

SUBJECT: [redacted] (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion (Empagliflozin only) of **Studies 1361.3** and **1361.11** (**NDA 212614**, Empaglif[redacted]-release [redacted] cted at [redacted] (b) (4).

I did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

Recommendation

Based on my review of the inspectional findings, I conclude the empagliflozin concentration data from the audited studies are reliable for FDA's review.

Inspected Studies

NDA 212614

Study Number: 1361.3

Study Title: "Bioequivalence of a fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)"

Sample Analysis Period: November 9 – 21, 2017

Methodology: LC-MS/MS

Study Number: 1361.11

Study Title: "Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open label, randomised, single-dose, two-period, two-sequence crossover study)"

Sample Analysis Period: November 7 – 19, 2018

Methodology: LC-MS/MS

Analytical Site: [redacted] (b) (4)

Scope of Inspection

OSIS scientist Yiyue [redacted] e anal [redacted] of above studies at [redacted] (b) (4) from [redacted] (b) (4) .

The previous analytical BIMO inspection covering in vitro studies conducted by [redacted] (b) (4) occurred from [redacted] (b) (4) and no Form FDA 483 was issued at the inspection close-out. The final classification was NAI. Prior to that, another analytical BIMO inspect [redacted] covering the a [redacted] f in vivo studies conducted by [redacted] (b) (4) occurred from [redacted] (b) (4) and no Form FDA 483 was issued at the inspection close-out. The final classification was NAI.

The current inspection of [redacted] (b) (4) included a thorough examination of study records, facilities, laboratory equipment, method validation, sample analysis (Empagliflozin only), and interviews with the firm's management and staff. Please note that the determination of Linagliptin and Metformin concentrations were conducted by [redacted] (b) (4)

[redacted] and [redacted], respectively.

Inspectional Findings

At the conclusion of the inspection, I did n conditions. I did not issue Form FDA 483 to [redacted].

Conclusion

After review of the inspectional findings, I conclude that empagliflozin concentration data from the audited studies are reliable for FDA review. Concentration data from studies using similar methods (LC/MS-MS) generated by [redacted] between the previous inspection covering the analytical portion of in vivo studies ([redacted]) and the end of the current surveillance interval should be considered reliable without an inspection.

Yiyue Zhang, Ph.D.
Staff Fellow

Final Classification:

Analytical Site

NAI – [redacted]

cc:
OTS/OSIS/Kassim/Dasgupta/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDBE/Bonapace/Au/Ayala/Biswas/Zhang
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Lewin

Draft: YZ 09/04/2019, 09/09/2019
Edit: RCA 9/05/2019, SA 9/5/2019, 9/9/2019

ECMS: Cabinets/CDER OTS/Office of Study Integri
ANALYTICAL/[redacted]

OSIS Fi[redacted]
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/11/2019

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212614

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in December 2017, which falls within the surveillance interval. The inspection was conducted under the following submissions: BLA (b) (4) and NDA (b) (4).

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations for BLA (b) (4):

- (b) (4)

After receiving a written response from the sponsor, OSIS recommended that all study data be accepted for Agency review but recommended that the primary review division evaluate whether ADA positive control stability data can be reliably interchanged among different animals species.

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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