CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208658
Supporting document/s:	SDN-000 (Initial submission)
Applicant's letter date (CDER Stamp Date):	2/10/16
Product:	Empagliflozin plus metformin XR FDC
Indication:	Type 2 diabetes mellitus
Applicant:	Boehringer Ingelheim
Review Division:	Metabolism and Endocrinology Products
Reviewer:	David B. Carlson, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director / Deputy Director:	Jean-Marc Guettier, M.D. James P. Smith, M.D.
Project Manager:	Michael White, Ph.D.
Review Completion Date:	10/28/16

Disclaimer

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Review Notes and Abbreviations/Key

Some of the sponsor's tables and figures from the electronic NDA submission have been included and cited in this review.

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1 Executive Summary

1.1 Introduction

Boehringer Ingelheim (BI) submitted NDA 208658 for a new extended release formulation of the approved combination of immediate release (IR) empagliflozin and metformin. Metformin extended release (XR) is currently listed as a monotherapy and as an extended release component in a similar once daily (QD) diabetes drug owned by BI (linagliptin and metformin XR; Jentadueto XR®). BI owns empagliflozin (NDA 204629), metformin XR as a component in linagliptin plus metformin XR (Jentadueto XR®, which was approved during the review cycle for this NDA), as well as immediate release empagliflozin plus metformin and linagliptin plus metformin fixed dose combination (FDC) products (NDA 206111 and NDA 201281). BI also cites a complete 'right of reference' to all information supporting the metformin extended release (metformin XR) drug substance and drug product information under NDA 21748 (GLUMETZA®).

1.2 Brief Discussion of Nonclinical Findings

No nonclinical data were included with the NDA. Nonclinical support for the safety of the proposed FDC tablets is claimed from cross-referencing information in approved drug products which BI owns or to which they have a written 'right of reference'. The drug substances in the proposed FDC tablets are identical to those previously approved. The drug product formulation is nearly identical to BI's recently approved linagliptin plus metformin XR FDC tablets (Jentadueto XR®). Clinical bioequivalence of the drug substances in the current formulation were confirmed.

There are no existing or new pharmacology or toxicology concerns about the listed drug substances proposed in the new FDC drug product. The pivotal nonclinical issues are the change in formulation compared to referenced immediate release empagliflozin plus metformin FDC and metformin XR monotherapy drugs and any potential impurities or novel excipients. The nonclinical review confirmed there are only minor differences in inactive ingredients and empagliflozin degradants in the proposed FDC drug product compared to listed drugs. Nonclinical review of the drug product excipients, including components of two (b) (4) film coatings not previously used in listed drug products, independently verified that there are no new excipients or impurities in the proposed drug product. Two theoretical empagliflozin degradants from the drug product were observed only under accelerated degradation conditions of high temperature or high temperature and high humidity. Nonclinical review confirmed empagliflozin degradants are not predicted to be genotoxic and drug product specifications are adequate to control potential degradant exposures and specifications comply with relevant ICH guidelines.

Proposed labeling is consistent with labeling for the listed monotherapy and FDC drugs. Labeling language has been updated to conform to the 'Pregnancy and Lactation

Labeling Rule' (PLLR).[1] Current Division and FDA/CDER recommendations for PLLR-compliant labels have been incorporated into the relevant nonclinical sections of the proposed drug label (see Section 1.3.3 Labeling below).

1.3 Recommendations

1.3.1 Approvability

Approval is recommended from a nonclinical perspective. Nonclinical data (cross-referenced from approved drugs) support the safe use of empagliflozin plus metformin extended release FDC tablets under the proposed uses.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Labeling updates have been discussed internally within the Division and with other FDA divisions prior to finalization of this Pharmacology/Toxicology Review and reviews in other disciplines. Specific nonclinical labeling recommendations are shown below.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

Based on animal data showing adverse renal effects from empagliflozin, TRADENAME is not recommended during the second and third trimesters of pregnancy.

Limited available data with TRADENAME or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. Empagliflozin was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

25 mg when administered during organogenesis. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20-25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and15-20%, respectively.

(b) (4)

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications.- (b) (4)

Poorly controlled diabetes increases the fetal risk for major birth defects, (b) (4) -still birth, and macrosomia related morbidity- (b) (4)

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups. (b) (4)

(b) (4)

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13 week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. In the rabbit, higher doses of empagliflozin

[2] Similar language with the combined drug components is included below the individual drug data in the empagliflozin and metformin FDC label (Synjardy®), which may be inconsistent with other diabetes FDC drug labels. Including the empagliflozin juvenile rat data at the beginning of the 'Animal Data' section highlights important empagliflozin findings in juvenile rats.

resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

(b) (4)

(b) (4)

Metformin hydrochloride: Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m^2) for rats and rabbits, respectively. (b) (4)

[3]

[3] Shaded portion of Sponsor's draft language (b) (4)

I recommend including it in this label although similar language does not seem to be included in a recent empagliflozin and metformin FDC label (Synjardy®).

Empagliflozin and Metformin: No adverse developmental effects were observed when empagliflozin and metformin were coadministered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

(b) (4)

[redacted]

8.2 Lactation

Risk Summary

There is no information regarding the presence of TRADENAME or empagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk *[see Data]*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Empagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of TRADENAME is not recommended while breastfeeding.

(b) (4)

[redacted]

(b) (4)

Data

(b) (4)

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Empagliflozin was present at a low level in fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 - 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

(b) (4)

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of TRADENAME in pediatric patients under 18 years of age have not been established.

2 Drug Information

2.1 Drug

Synjardy XR® (tentatively approved 4/22/16)
Empagliflozin and metformin HCl extended release (XR) FDC film coated tablets

2.1.1 CAS Registry Number

Empagliflozin – 864070-44-0
Metformin HCl – 115-70-4 [Metformin (free base) – 657-24-9]

2.1.2 Generic Name

Empagliflozin / metformin HCl XR

2.1.3 Code Name

Empagliflozin (BI 10773 XX)
Metformin

2.1.4 Chemical Name

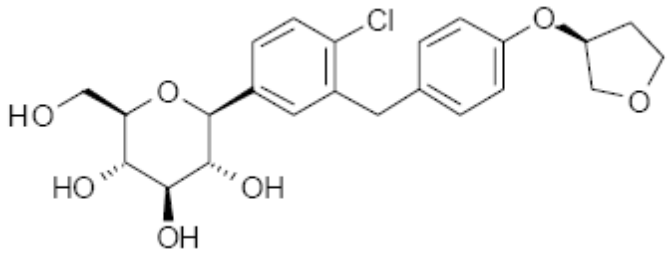
Empagliflozin: (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol
Metformin HCl: 1,1-dimethylbiguanide hydrochloride;
N,N-Dimethylimidodicarbonimidic diamide hydrochloride

2.1.5 Molecular Formula/Molecular Weight

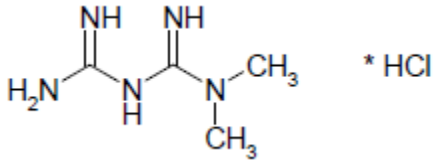
Empagliflozin – $C_{23}H_{27}ClO_7$ / 450.91 g/mol
Metformin HCl – $C_4H_{12}ClN_5$ / 165.6 (b) (4) g/mol

2.1.6 Structure (or Biochemical Description)

Empagliflozin



Metformin HCl



2.1.7 Pharmacologic class

Sodium glucose co-transporter 2 (SGLT2) inhibitor (empagliflozin) /
Biguanide (metformin HCl)

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 111919 – Empagliflozin / metformin HCl XR
NDA 204629 – Empagliflozin (Jardiance®)
NDA 201281 – Metformin HCl (from linagliptin/metformin FDC, Jentadueto®)
DMF (b) (4) – Metformin HCl
NDA 021748 – Metformin HCl extended release (GLUMETZA®)
NDA 206111 – Empagliflozin / metformin HCl (Synjardy®)
NDA 208026 – Linagliptin / metformin HCl XR (Jentadueto XR®)
Reviewer's note – the linagliptin/metformin HCl XR (Jentadueto XR®) NDA was not explicitly cross-referenced for the extended release tablet formulation but the Sponsor owns that drug and drug product formulation information relevant to this NDA was referenced by this Reviewer

2.3 Drug Formulation

Empagliflozin and metformin HCl drug substances are manufactured as previously described for listed drugs. The drug product is manufactured as film coated tablets containing fixed dose combinations of immediate release empagliflozin and extended release metformin, developed for once daily oral administration. Several tablet formulations containing 5 mg to 25 mg empagliflozin and 1000 mg or 2000 mg metformin were designed to allow individual patient dose titration up to the maximum recommended daily doses of 25 mg empagliflozin and 2000 mg metformin (Sponsor's Table 1).

Table 1 – Key dug product information and dosing regimen

Key information for empagliflozin / metformin hydrochloride extended release (ER) coated tablets

Name of the drug product:	Empagliflozin / metformin hydrochloride extended release (ER) coated tablets
Drug substances:	Empagliflozin Metformin hydrochloride
Company:	Boehringer Ingelheim
Dosage form:	Tablets (extended release coated tablets)
Indication:	Adult patients with type 2 diabetes mellitus
Strengths:	5 mg/1000 mg, 10 mg/1000 mg, 12.5 mg/ 1000 mg and 25 mg/1000 mg empagliflozin/metformin hydrochloride
Route of administration:	Oral use

Dosing regimen and daily dose	Tablet strength	Posology	Daily dose (empagliflozin)	Daily dose (metformin HCl)
	5 mg / 1000 mg	2 tablets once daily	10 mg	2000 mg
	10 mg / 1000 mg	1 tablet once daily	10 mg	1000 mg
	12.5 mg / 1000 mg	2 tablets once daily	25 mg	2000 mg
	25 mg / 1000 mg	1 tablet once daily	25 mg	1000 mg

Reviewer's note – maximum recommended human dose is 25 mg empagliflozin and 2000 mg daily

A schematic of the drug product, consisting of a metformin HCl extended release core and an immediate release layer of empagliflozin is shown in the Sponsor's Figure 1. The extended release metformin core and immediate release [redacted] (b) (4) tablet design is similar to that used in the sponsor's approved linagliptin and metformin XR tablets (Jentadueto XR®).

(b) (4)

The Sponsor's summaries of inactive ingredients in the film coated tablets are shown in Table 2 and, Table 3 below. The Sponsor stated the drug product formulation "uses excipients (or, for (b) (4) film-coating systems, (b) (4)) that are commonly used in similar proportions in approved oral drug products. All excipients meet regulatory and compendial requirements." An independent analysis of the drug product formulation by this Pharmacology/Toxicology Reviewer confirmed that all listed excipients are found in FDA's public Inactive Ingredients Guide (IIG)[4], with the exception of (b) (4) commercial products. The individual components in the different (b) (4) commercial formulations were provided and all compounds were found in similar oral products described in the IIG with the exception of polydextrose in (b) (4) (Table 3). Polydextrose is listed in oral drugs in the IIG at up to (b) (4) per tablet. Polydextrose is a non-digestible polysaccharide approved for use as a food additive under several conditions without a restriction on daily intake.[5] Polydextrose ingestion has also been determined to be 'generally recognized as safe' (GRAS) by experts and regulatory agencies for a variety of uses including in food and as a laxative at levels of several g per day (e.g., see review by Flood et al., 2004).[6] The slightly higher level of (b) (4) polydextrose per tablet contained in the drug product compared to listed drugs does not add appreciably to estimated daily human exposures and does not pose a safety concern.

[4] U.S. Food and Drug Administration, Inactive Ingredient Search for Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm, accessed 10/27/16
[5] 21 CFR 172.841
[6] Flood MT, Auerbach MH, Craig SA. 2004. A review of the clinical toleration studies of polydextrose in food. Food Chem Toxicol, 42(9):1531-42.

Table 2 – Drug product composition

Qualitative and Quantitative Composition of Empagliflozin/ Metformin HCl ER Coated Tablets

Ingredient	5 mg / 1000 mg	10 mg / 1000 mg	12.5 mg / 1000 mg	25 mg / 1000 mg	Function	Reference to Standards
	[mg / tablet]					
Tablet Core						
Metformin HCl[1]	1000.0	1000.0	1000.0	1000.0	Drug substance	USP
Polyethylene Oxide (b) (4)	(b) (4)					NF[2]
Hypromellose (b) (4) (b) (4)						USP
Magnesium Stearate (b) (4						NF
						USP
						(b) (4)
Empagliflozin (b) (4)					(b) (4)	Company Standard
						Company Standard
Polyethylene Glycol (b) (4)						NF
Talc						USP
Purified Water						USP

(cont'd) Qualitative and Quantitative Composition of Empagliflozin/ Metformin HCl ER Coated Tablets

Ingredient	5 mg / 1000 mg	10 mg / 1000 mg	12.5 mg / 1000 mg	25 mg / 1000 mg	Function	Reference to Standards
	[mg / tablet]					
(b) (4) Film-Coat						
(b) (4) Green (b) (4)					(b) (4)	Company Standard
(b) (4) Orange (b) (4)						Company Standard
(b) (4) Blue (b) (4)						Company Standard
(b) (4) Green (b) (4)						Company Standard
Purified Water						USP/Ph.Eur.
(b) (4)						(b) (4)
(b) (4)					(b) (4)	Company Standard
Carnauba Wax						NF
Purified Water						USP
(b) (4)						(b) (4)
(b) (4) Black					(b) (4)	Company Standard
Isopropyl Alcohol						USP
Total mass	1606.9	1611.9	1614.4	1526.9		
(b) (4)						(b) (4)

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2.4 Comments on Novel Excipients

No novel excipients are used in the drug product and all excipients listed in the drug product information meet regulatory and compendial requirements.

2.5 Comments on Impurities/Degradants of Concern

All drug substance impurities were assessed in reviews of drug substances cross-referenced for this FDC application. No residual solvents or degradation products of

empagliflozin or metformin HCl above reporting thresholds were observed in release testing of FDC tablets.

No metformin HCl drug product degradation products were identified above the reporting threshold of (b) (4)% under either normal or accelerated storage conditions. A transient peak representing an unspecified degradation product at (b) (4)% was seen in three month but not later time points for the 12.5 mg/1000 mg tablets. The peak was considered an artifact by the Sponsor since it was seen in only one dosage strength at only one early time point.

Two empagliflozin degradation products were identified from drug product at elevated temperature (50°C in closed bottles) and under accelerated stability testing (40°C and 75% relative humidity (RH)). Degradants were identified as (b) (4) which represent (b) (4) empagliflozin, respectively (Table 4). The degradants were only observed from the 5 mg / 1000 mg (empagliflozin / metformin HCl XR) tablets.

Both (b) (4) were found to be non-mutagenic by computation structure activity relationship (SAR) screening by the Sponsor. Both degradants were assessed in accordance with ICH M7 'Mutagenic Impurities' Guidance for Industry.[7] The SAR analyses included expert knowledge-based analysis (DEREK v Nexus 4.1.0) and statistical based analysis (Sarah v 1.2.0). Both degradants are considered Class 5 impurities ("treat as non-mutagenic impurity") and require no specific action for control of the degradants in the drug product.[8] The (b) (4)% specification limit for each degradant in the drug product is within the applicable ICH Q3B qualification thresholds for the maximum daily dose of 25 mg empagliflozin.[9]

[7] International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2015. M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Guidance for Industry.
[8] *IBID*
[9] See Quality review for this NDA 208658.

Table 4 – Empagliflozin degradation products (accelerated storage conditions)

Degradation Products of Empagliflozin

2.6 Proposed Clinical Population and Dosing Regimen

Fixed dose empagliflozin and metformin XR is indicated for adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in patient (b) (4)

2.7 Regulatory Background

This is the original submission for empagliflozin/metformin XR tablets. All drug substances have been previously approved and the Sponsor owns, or has a written 'right of reference' to, all of the drug substances and drug product components.

3 Studies Submitted

3.1 Studies Reviewed

None. No nonclinical data were submitted with the application. All nonclinical information is incorporated by cross-reference from other applications.

3.3 Previous Reviews Referenced

Carlson DB. NDA 208026, Pharmacology/Toxicology Review, 5/4/16.
Carlson DB. NDA 201281, Pharmacology/Toxicology Review, 10/4/11.
Summan M. NDA 206111, Pharmacology/Toxicology Review, 4/15/15.

4 Pharmacology

4.1 Primary Pharmacology

Empagliflozin is a reversible, competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2); IC_{50} = 1.3 nM in vitro. Empagliflozin shows approximately 5000-fold selectivity for SGLT2 inhibition compared to SGLT1 inhibition (IC_{50} = 6278 nM). SGLT2 is localized to kidney proximal tubules where it facilitates reuptake of glucose prior to excretion in urine. Inhibition of SGLT2 prevents glucose reuptake in proximal tubules and results in increased glucose excretion, or glucosuria.

Metformin pharmacology is still not entirely understood but it seems to improve insulin sensitivity at peripheral target tissues including liver, muscle, and adipose. Metformin does not seem to directly affect insulin production or metabolism, but treatment increases glucose uptake and utilization in peripheral tissues, decreases hepatic glucose production, and decreases intestinal glucose absorption.

11 Integrated Summary and Safety Evaluation

The proposed empagliflozin plus metformin XR FDC tablet NDA was submitted in accordance with 21 USC 505(b)(1) for treatment of type 2 diabetes mellitus. No nonclinical studies were submitted. An integrated summary of nonclinical information of individual drug substances and empagliflozin plus metformin immediate release coadministration studies was provided. The Sponsor relied on cross-referencing existing nonclinical data from several listed individual and FDC drugs.

Pivotal nonclinical review issues were limited to potential impurities and novel excipients. The drug substances are identical to listed drugs and the drug product is only slightly modified from the listed empagliflozin plus metformin IR FDC and the listed metformin XR monotherapy (GLUMETZA®) and FDC (Jentadueto XR®) drug products. The Pharmacology/Toxicology review did not identify any new safety concerns. No novel excipients or unqualified impurities were identified.

Clinical bioavailability/bioequivalence studies confirmed similar pharmacokinetic profiles for empagliflozin and metformin compared to individual drug substances and the listed empagliflozin plus metformin immediate release formulation. Pharmacology and toxicology studies conducted with empagliflozin, metformin, and empagliflozin/metformin coadministration support proposed use of the new extended release FDC clinical formulation.

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

/s/

DAVID B CARLSON
11/07/2016
Nonclinical Review - Approval recommendation

TODD M BOURCIER
11/07/2016
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA No.: NDA 208658 **Applicant:** Boehringer Ingelheim **Stamp Date:** 2/10/16

Drug Name: Empagliflozin/ metformin XR FDC **NDA/BLA Type:** 505(b)(1)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	N/A		No new pharmacology/toxicology information was provided. The Sponsor is relying on data from previously approved drugs.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		Pharmacology/toxicology information relied on for safety determination is summarized in a Nonclinical Overview, Section 2.4. No Nonclinical Section 4 was included in the eCTD.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	N/A		Pre-NDA meeting correspondence shows DMEP communication that no new nonclinical data would be submitted and nonclinical support would be based on cross-reference to previously approved drug products, including the empagliflozin/metformin FDC (Synjardy®).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	N/A		Oral route of exposure is consistent with monotherapy and empagliflozin/metformin FDC routes.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		Combination empagliflozin/metformin toxicity studies were required based on pre-IND correspondence. Studies were submitted and reviewed in support of the empagliflozin/metformin FDC drug product under NDA 206111 (approved as Synjardy®).
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Draft label submitted to comply with PLLR. Final label will be based on current Synjardy® label and ongoing revisions and PLLR update in response to a NDA supplement currently under review.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Sponsor notes in the 'Reviewer Guide' that no impurities or degradants specific to empagliflozin/metformin XR were predicted to be mutagenic or were observed above ICH Q3B qualification thresholds. Adequacy of impurity and degradant characterization will be a review issue.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A		
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	N/A		Sponsor owns drug information or has provided a written right of reference for all drug substances in this 505(b)(1) application.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

No potential review issues were identified for inclusion in the 74-day letter.

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/s/

DAVID B CARLSON
03/23/2016
NDA is fileable from a nonclinical perspective.

TODD M BOURCIER
03/23/2016
I concur