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APPLICATION NUMBER:

208658Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(1) New Drug Application
Application Number(s)	NDA-208658
Priority or Standard	Standard
Submit Date(s)	February 10, 2016
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PDUFA Goal Date	December 9, 2016
Division / Office	DMEP
Reviewer Name(s)	Andreea O. Lungu
Review Completion Date	November 9, 2016
Established Name	Empagliflozin-Metformin extended release
Trade Name	Synjardy XR
Therapeutic Class	Sodium-dependent glucose co-transporter-2 inhibitor
Applicant	Boehringer Ingelheim Pharmaceuticals Inc.
Formulation(s)	Tablet
Dosing Regimen	5mg / 1000mg, 10mg / 1000mg, 12.5mg / 1000mg, and 25mg / 1000mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate.
Intended Population(s)	Adults with Type 2 Diabetes Mellitus
Team Leader	William H. Chong
Division Director	Jean-Marc Guettier
Statistical Reviewer - Efficacy	Jennifer Clark
Project Manager	Michael G. White

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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BE	Bioequivalence
CHF	Congestive heart failure
CI	Confidence interval
CMQ	Customized MedDRA query
CV	Cardiovascular
CVOT	Cardiovascular outcomes trial
CTD	Common technical document
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DPP-4	Dipeptidyl peptidase-4
DSC	Drug Safety Communication
eCTD	Electronic Common Technical Document
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
Empa	Empagliflozin
ER	Extended release
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term
ICH	International Conference on Harmonisation
ICH E3	International Conference on Harmonisation: Structure and content of clinical study reports
IND	Investigational new drug

IR	Immediate release
MACE	Major adverse cardiovascular event
MAED	MedDRA Adverse Event Diagnostics
MedDRA	Medical Dictionary for Regulatory activities
MI	Myocardial infarction
NA	Not applicable
NDA	New Drug Application
PG	Plasma glucose
PI	Principal investigator
PK	Pharmacokinetics
PT	Medical Dictionary for Regulatory Activities Preferred Term
SAE	Serious adverse event
SBP	Systolic blood pressure
SGLT2	Sodium-dependent glucose co-transporter-2
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	Medical Dictionary for Regulatory Activities System Organ Class
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TZD	Thiazolidinedione

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant has submitted a 505(b)(1) New Drug Application (NDA) for a fixed drug combination (FDC) of empagliflozin and metformin hydrochloride extended release (ER) tablets for use once daily in patients with Type 2 diabetes mellitus (T2DM). Empagliflozin (NDA 204629) and metformin ER (NDA 21748) are FDA approved for use in patients with T2DM. In addition, an FDC of empagliflozin and metformin immediate release (NDA 206111) is approved for use in patients with T2DM. To support this FDC product, the applicant has conducted clinical pharmacology studies to establish bioequivalence of empagliflozin and metformin hydrochloride extended- release fixed dose combination tablets to the single entity components in healthy volunteers. The applicant proposes that the safety and efficacy information previously reviewed and approved in prescribing information for Synjardy (empagliflozin and metformin hydrochloride immediate release) tablets, Glumetza (metformin extended-release tablets) tablets, and Jardiance (empagliflozin), supports the safety and efficacy of this formulation.

(b) (4)

The applicant has proposed the following indications for the Synjardy XR product:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate.

I am recommending approval of this NDA. The contribution of metformin and of empagliflozin to the claimed effect of glycemic lowering has been demonstrated in clinical trials (see reviews and labeling for Synjardy [NDA 206111]), and I believe that these data can be used to support this NDA.

1.2 Risk Benefit Assessment

For in depth discussion of the risk-benefit of this empagliflozin and metformin combination with regard to the glycemic control indication, see the clinical review from the initial NDA review for Synjardy (NDA 206111). In brief, data from clinical studies supported that the combination of

empagliflozin and metformin improved glycemic control and that the safety profile was consistent with what would be expected by combining the two drug products. The risk-benefit conclusions for this NDA are the same, and thus I conclude that there is a favorable risk-benefit for the proposed glycemic control indication.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Type 2 diabetes mellitus is a disease of impaired glucose homeostasis and chronic hyperglycemia. Management of T2DM focuses on glycemic control, and involves lifestyle changes (diet and exercise) as well as use of currently available antidiabetic drugs.

Empagliflozin is a sodium-dependent glucose co-transporter-2 (SGLT2) inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, a disease of impaired glucose regulation due to impaired insulin action and insulin resistance. SGLT2 is a transporter found in the proximal renal tubule, and is responsible for renal glucose reabsorption. Inhibition of this transporter increases glucosuria, which in turn results in improved glycemic control. (b) (4)

(b) (4)

Metformin is a biguanide approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. By decreasing hepatic gluconeogenesis, and improving peripheral insulin sensitivity leading to increased peripheral glucose uptake and utilization, metformin lowers plasma glucose levels. Metformin is available in both immediate release and extended release forms.

This fixed dose combination drug product (FDC) combines empagliflozin and metformin extended release into a single tablet. As mentioned previously, a fixed drug combination product combining empagliflozin and metformin immediate release is already approved as Synjardy, for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

2.1 Currently Available Treatments for Proposed Indications

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, many of these drug classes may be poorly tolerated or have limited usefulness in certain populations. For example, sulfonylureas (SU) and insulin are associated with a high risk for hypoglycemia, thiazolidinedione's (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors are contraindicated in patients with severe renal dysfunction. TZDs, SUs, and insulin are all associated with significant weight gain. Additionally, progressive β-cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time requiring the addition of other agents. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies and concomitant treatment options for T2DM in patients who are not adequately controlled on monotherapy.

The current NDA does not propose a novel approach to diabetes management, but rather combines two drug products already approved for use in improving glycemic control in patients with type 2 diabetes in a fixed dose combination.

2.2 Availability of Proposed Active Ingredient in the United States

Empagliflozin, metformin IR and ER, and the empagliflozin + metformin IR combination drug product are approved for marketing in the United States, and are available by prescription.

2.3 Important Safety Issues with Consideration to Related Drugs

There are three SGLT2 inhibitors currently approved by the FDA: empagliflozin, dapagliflozin, and canagliflozin.

Safety concerns believed to be related to the drug class include hypotension, diabetic ketoacidosis (DKA), urosepsis and urinary tract infections, genital mycotic infections, decreases in renal function, and increases in hematocrit and cholesterol. Recently, serious concerns regarding a potential for ketoacidosis and serious urinary tract infections have been identified, resulting in a safety labeling change for all approved SGLT2 inhibitors on December 4, 2015

A numerical increase in stroke events was also seen with all members of the class, however not statistically significant.

A few safety signals are ongoing evaluation: fractures and amputations. An increase in the incidence of upper extremity fractures was seen with canagliflozin. Also, recently, canagliflozin was found to result in an increase in lower extremity amputations in patients at risk. It is not clear whether these signals will withstand time and whether they are a class effect.

Safety concerns with metformin include:

- Lactic acidosis
- Diarrhea
- Nausea
- Vitamin B12 deficiency
- Hypoglycemia with concomitant insulin or insulin secretagogue therapy

2.4 Summary of Presubmission Regulatory Activity Related to Submission

Previous FDA regulatory interactions included a pre-IND Type B meeting (submitted May 25, 2011) and a subsequent Type C meeting (submitted December 23, 2013) regarding the development of this FDC. On October 11, 2011 and March 10, 2014, the Division provided written responses to the meeting requests BI submitted.

Briefly, the Division asked that in vivo bioequivalence should be shown for all tablet strengths under fed conditions. If bioequivalence for a tablet strength could be established after single-dose administration, bioequivalence after multiple-dose administration would not be necessary. The Division also agreed to the use of Glumetza 500 mg as a reference product for the bioequivalence studies, since the empagliflozin/metformin XR FDC formulations are based on the same system used in Glumetza 500 mg. In March 2014, general agreement was reached that a biowaiver for the two lower FDC strengths (5/1000 mg and 12.5/1000 mg) will be submitted with the NDA, as long as the tested doses showed bioequivalence.

On 16 Jul 2015, the Division provided written responses to the questions posed in the pre- NDA meeting package. Agreements were reached on the proposed content and format of the Modules 2 to 5 of the NDA, the electronic submission plan, and the proposed content of the 4-month safety update. Regarding the clinical documents in the NDA, the Division agreed to the applicant's proposal of cross-referencing the existing clinical safety and efficacy data for empagliflozin (Jardiance; NDA 204629), the combination of empagliflozin/metformin IR (Synjardy NDA 206111), and metformin XR (Glumetza NDA 021748). The Division agreed to the applicant's proposal that clinical summaries (Module 2.7) or integrated summaries of efficacy and safety (ISE/ISS) are not required as only Phase I studies have been conducted for this NDA.

The Division agreed that the 4-month safety update would be prepared using any relevant postmarketing data and medical literature data from Synjardy. In addition, FDA requested a summary safety report with information from Jardiance.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was acceptable. All of the clinical studies referenced to support this NDA have been previously reviewed under other NDAs. Review of the quality and integrity of the clinical pharmacology studies is deferred to the clinical pharmacology reviewer. There are no apparent issues with data integrity or with the integrity of study conduct.

3.2 Compliance with Good Clinical Practices

The Applicant states that the clinical pharmacology studies submitted in support of this NDA were conducted in compliance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), and conformed to the Declaration of Helsinki, as well as applicable regulatory requirements, and relevant local

guidelines. An on-site inspection was arranged by the Office of Study Integrity and Surveillance for the clinical portion of the bioequivalence study 1276.28 and no deficiencies were observed.

3.3 Financial Disclosures

All the seven investigators for the bioequivalence studies 1276.15 and 1276.28 are applicant employees as typical in this type of study. No significant concerns have been identified based on review of the financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review recommends approval, based on the information submitted to the NDA. For detailed discussion, see Dr. Suong Tran's review.

The information below briefly summarizes the applicant's submitted CMC information for the drug product.

Empagliflozin/metformin ER drug product is a film coated tablet for oral administration. Empagliflozin/metformin ER coated tablets consist of a metformin HCl release tablet core that is (b) (4), one of which contains empagliflozin.

The applicant developed four strengths of the FDC as shown in Table 1, and they can be differentiated by the color of the film coat and by imprint. .

Table 1 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

Source: Table 1 Quality Overall Summary, NDA 208658 original submission

4.2 Clinical Microbiology

There is no information related to clinical microbiology included in this supplement.

4.3 Preclinical Pharmacology/Toxicology

There is no new pharmacology/toxicology information included in this supplement.

4.4 Clinical Pharmacology

Please see the review by Dr. Ritesh Jain for detailed discussion of the clinical pharmacology studies. Based on the results of the clinical pharmacology studies, Dr. Jain recommends approval of this NDA.

The following clinical pharmacology studies have been submitted by the applicant:

Study no	**Objective and Description**	**FDC dose tested (mg)**	**Free combination dose tested (mg)**
1276.13	Relative bioavailability, single-dose, pilot study	Empa25/Met XR 1000	Empa 25 + 2xMet XR 500
1276.14	Relative bioavailability, single-dose, pilot study	Empa10/Met XR 1000	Empa 10 + 2xMet XR 500
1276.15	Relative bioavailability, single-dose, pivotal study	Empa25/Met XR 1000	Empa 25 + 2xMet XR 500
1276.28	Relative bioavailability, single-dose, pivotal study	Empa10/Met XR 1000	Empa 10 + 2xMet XR 500

There were two pivotal clinical Phase I trials conducted with empagliflozin/metformin ER coated tablets. Both of these trials were bioequivalence studies comparing empagliflozin/metformin ER coated tablets to the free combination of empagliflozin immediate release coated tablets and Glumetza 500 mg (metformin ER tablets). Both pivotal studies were performed under fed conditions. The proposed commercial formulation with the dose strengths of 10 mg/1000 mg and 25 mg/1000 mg was used in these studies.

The phase I pivotal studies have demonstrated bioequivalence (BE) for the tablet strengths tested (10 mg/1000 mg and 25 mg/1000 mg) which support bridging of the existing safety and efficacy data from clinical studies with empagliflozin (Jardiance; NDA 204629), the combination of empagliflozin/metformin IR (Synjardy, NDA 206111) and metformin extended release (Glumetza NDA 021748) to the proposed extended release FDC. Both studies were performed

in healthy volunteers under fed conditions. In each study, a randomized, open-label, 2-way crossover design was used. The wash-out period between the 2 treatments was at least 7 days.

The applicant states that in both studies, the bioequivalence of empagliflozin and metformin was determined based on the pharmacokinetic parameters AUC0-tz and Cmax. An analysis of variance (ANOVA) model on the logarithmic scale was used for the statistical evaluation. The model included the random effect 'subjects within sequences' and the fixed effects 'sequence', 'period', and 'treatment'. The acceptance range for bioequivalence was 80.00 to 125.00%, based on 2- sided 90% confidence intervals (CIs) for the ratio of the geometric means (gMeans; FDC vs. free combination) of the parameters.

Biowaivers are requested for the two additional FDC strengths (5 mg/1000 mg and 12.5 mg/1000 mg).

These bioavailability studies have been reviewed by Dr Jain, please see clinical pharmacology review for details. Overall, Dr. Jain concludes that the FDC formulations are bioequivalent to the co-administration of the individual components (for which clinical efficacy has been previously established).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

To support safety and efficacy of this empagliflozin/metformin ER FDC tablet, the applicant cross-refers to the safety and efficacy information previously reviewed and approved in prescribing information for Synjardy (empagliflozin and metformin hydrochloride) tablets, Glumetza (metformin extended-release tablets) tablets, and Jardiance (empagliflozin).

The efficacy and safety of combining empagliflozin and metformin has been studied as part of the Phase 3 clinical trials in support of NDA 204629 (Jardiance) and NDA 206111 (Synjardy). These included an add-on combination therapy of empagliflozin with metformin study, add-on combination therapies of empagliflozin with metformin and other antidiabetic drugs (including insulin), and a study of dual initial combination therapy of empagliflozin and metformin. For a detailed description of these studies, see the clinical reviews dated November5, 2013, May 14, 2015, February 5, 2016in NDA 204629 and dated June 4, 2015 and February 5, 2016 in NDA 206111. (b) (4)

The primary new data that applicant submitted to support this NDA are the following clinical pharmacology studies:

Study no	Objective and Description	FDC dose tested (mg)	Free combination dose tested (mg)
1276.13	Relative bioavailability, single-dose, pilot study	Empa25/Met XR 1000	Empa 25 + 2xMet XR 500
1276.14	Relative bioavailability, single-dose, pilot study	Empa10/Met XR 1000	Empa 10 + 2xMet XR 500
1276.15	Relative bioavailability, single-dose, pivotal study	Empa25/Met XR 1000	Empa 25 + 2xMet XR 500
1276.28	Relative bioavailability, single-dose, pivotal study	Empa10/Met XR 1000	Empa 10 + 2xMet XR 500

5.2 Review Strategy

No Phase 3 clinical studies investigating the efficacy of empagliflozin/metformin extended release FDC were conducted. The applicant cross-referenced the safety and efficacy data from NDAs previously reviewed for approval of Jardiance, Glumetza, and Synjardy to provide support for the clinical efficacy and safety of this NDA.

The new clinical data for this NDA comes from the Phase 1 BE studies listed in Section 5.1.

For my discussion of safety, I am presenting the safety data from the new Phase 1 BE studies and the 4-month Safety Update. (b) (4)

5.3 Discussion of Individual Studies/Clinical Trials

No new Phase 3 trials specific to the proposed FDC are submitted; see section 4.4 for brief discussion and Clinical Pharmacology review by Dr. Jain for details regarding clinical pharmacology studies.

6 Review of Efficacy

Efficacy Summary

No new clinical efficacy studies were submitted to support the proposed combination of empagliflozin and metformin XR. The efficacy for individual component was established under Jardiance for empagliflozin (NDA 204629) and Glumetza for metformin extended release (NDA 021748), and the clinical efficacy for combination therapy of empagliflozin and metformin IR

has been established under Synjardy (NDA 206111). Metformin IR and ER have been previously shown to have similar efficacy. Therefore, the clinical development program for this FCDP was based on clinical pharmacology studies to bridge the existing clinical efficacy and safety data by demonstrating the bioequivalence of the FCDP tablets to the co-administration of individual components in healthy volunteers in pivotal Phase 1 bioequivalence (BE) studies. The review of the results of these BE studies can be found in Dr. Jain review dated November 3, 2016.

In brief, the clinical studies have shown that each of the components contributes to the claimed effect of improving glycemic control. See the clinical reviews from NDA 206111 (submitted by Dr. Chong on August 24, 2015 and submitted by this reviewer on June 1, 2016) and the statistical reviews by Dr. Shuxian Sinks (submitted on April 16, 2015 and February 12, 2016) for details of the efficacy results.

6.1 Indication

The Applicant proposes the following indication for this FDC:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate.

7 Review of Safety

Safety Summary

The safety of combining empagliflozin and metformin has been reviewed in detail as part of the initial review of NDA 206111. The safety of combining empaglifozin and metformin is consistent with what would be expected based on the safety profiles of the individual drugs. In brief, the adverse reaction profile is consistent with what would be seen by combining the two drug products. No synergistic effects were seen. See the clinical reviews from NDA 206111 (submitted by Dr. Chong on August 24, 2015 and submitted by this reviewer on June 1, 2016)

The safety of the phase 1 bioequivalence studies is briefly summarized over the next few sections. In summary, no deaths or SAEs occurred in these studies, as well as no significant adverse events.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

No clinical study investigating the safety of empagliflozin/metformin XR FDC was conducted as was agreed upon with the Division. The safety from the four phase 1 studies looking at the co-administration of empagliflozin and metformin XR either as FDC or as free combinations, in addition to the 4 month safety update, are the focus of this review.

7.1.2 Categorization of Adverse Events

Per the applicant, for the phase 1 studies submitted, MedDRA 17.1 was used for coding of the adverse events. The coding of the adverse events were confirmed by the clinical trial monitor.

7.2 Adequacy of Safety Assessments

The safety assessments are adequate for the proposed NDA. As described above, the majority of safety data related to combined empagliflozin and metformin use were evaluated during Jardiance and Synjardy NDA review, as well as efficacy supplements for the respective NDAs. Safety data from Phase 1 clinical studies in healthy volunteers and updated safety data are reviewed here for completeness.

Reviewer comment: The safety information from this submission does not add much to the safety of empagliflozin, metformin, or the empagliflozin/metformin combination drug product.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the four new Phase 1 clinical pharmacology studies.

7.3.2 Nonfatal Serious Adverse Events

No SAEs were reported in any of the four new Phase 1 clinical pharmacology studies.

7.3.3 Dropouts and/or Discontinuations

None.

7.3.4 Significant Adverse Events

None

7.3.5 Submission Specific Primary Safety Concerns/Adverse Events of Special Interest

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 1276.13

A total of 14 out of 71 subjects (19.7%) reported AEs during the treatment periods. The most frequent AE was headache, which occurred to 6 subjects (8.5%) in total, followed by nausea (5 subjects (7.0%). Abdominal pain and diarrhea were reported in 3 subjects (4.2%) each in total and vomiting occurred in 2 subjects (2.8%) in total. All adverse events were mild or moderate in intensity.

Study 1276.14

A total of 34 out of 72 subjects (47.2%) reported AEs during the treatment periods. The majority of the AEs were of mild intensity, only two AEs (nausea and vomiting) in one subject were of moderate intensity. The most frequent AE was diarrhea, which occurred in 10 subjects (13.9%) , the second most AE was nausea, which was reported for 8 subjects (11.1%). Dizziness was reported for 7 subjects (9.7%), abdominal pain was reported in 6 subjects (8.3%), and headache was reported in 5 subjects (6.9%). All other AEs were reported in less than 5 subjects on treatment

Study 1276.15
Twelve out of 30 treated subjects (40.0%) reported at least 1 adverse event during the on-treatment periods of the trial. Two subjects reported “presyncope” which was a designated AESI, however they happened prior to any trial drug intake (during screening). An overview of the on-treatment adverse events by primary system organ class and preferred term is presented below.

Table 2 Frequency of subjects with on-treatment adverse events by primary system organ class and preferred term - TS

SOC/ preferred term	Treatment R (single tablets) N (%)	Treatment T (FDC) N (%)	Total on-treatment N (%)
Number of subjects	30 (100.0)	30 (100.0)	30 (100.0)
Nervous system disorders	3 (10.0)	2 (6.7)	5 (16.7)
Headache	3 (10.0)	2 (6.7)	5 (16.7)
Gastrointestinal disorders	2 (6.7)	2 (6.7)	2 (6.7)
Diarrhoea	2 (6.7)	1 (3.3)	2 (6.7)
Abdominal pain	0	1 (3.3)	1 (3.3)
Infections and infestations	0	2 (6.7)	2 (6.7)
Nasopharyngitis	0	2 (6.7)	2 (6.7)
Respiratory, thoracic and mediastinal disorders	1 (3.3)	1 (3.3)	2 (6.7)
Cough	1 (3.3)	1 (3.3)	2 (6.7)
Musculoskeletal and connective tissue disorders	1 (3.3)	0	1 (3.3)
Pain in extremity	1 (3.3)	0	1 (3.3)
Metabolism and nutrition disorders	1 (3.3)	0	1 (3.3)
Decreased appetite	1 (3.3)	0	1 (3.3)

System organ class terms and preferred terms were sorted, if possible, according to the frequency of their occurrence in total.

Source: Table 12.1.2: 1 1276.15 study report

Study 1276.28

Fourteen of the 30 treated subjects (46.7%) reported at least one adverse event during the on-treatment period of the trial. One subject was reported with AESI pollakiuria (project-defined AESI) during his first treatment period. All adverse events were reported as mild to moderate in intensity. During the on-treatment periods, the most frequently reported adverse events overall at the SOC level were nervous system disorders (7 subjects, 23.3%), followed by gastrointestinal disorders (5 subjects, 16.7%) and infections/infestations (2 subjects, 6.7%). On the preferred term level, the most frequent adverse events were headache (7 subjects, 23.3%) as well as diarrhea, nausea, and nasopharyngitis (2 subjects, 6.7% each). All other adverse events were reported by only 1 subject (3.3%) each.

Table 3 Frequency of subjects with on-treatment adverse events by primary system organ class and preferred term - TS

SOC/ preferred term	Treatment R (single tablets) N (%)	Treatment T (FDC) N (%)	Total on-treatment N (%)
Number of subjects	30 (100.0)	30 (100.0)	30 (100.0)
Nervous system disorders	5 (16.7)	4 (13.3)	7 (23.3)
Headache	5 (16.7)	4 (13.3)	7 (23.3)
Dizziness	1 (3.3)	0	1 (3.3)
Gastrointestinal disorders	4 (13.3)	3 (10.0)	5 (16.7)
Diarrhoea	2 (6.7)	1 (3.3)	2 (6.7)
Nausea	2 (6.7)	0	2 (6.7)
Abdominal distension	0	1 (3.3)	1 (3.3)
Vomiting	0	1 (3.3)	1 (3.3)
Infections and infestations	1 (3.3)	1 (3.3)	2 (6.7)
Nasopharyngitis	1 (3.3)	1 (3.3)	2 (6.7)
Renal and urinary disorders	0	1 (3.3)	1 (3.3)
Pollakiuria	0	1 (3.3)	1 (3.3)
Reproductive system and breast disorders	1 (3.3)	0	1 (3.3)
Dysmenorrhoea	1 (3.3)	0	1 (3.3)

Please note that system organ class terms and preferred terms were sorted, if possible, according to the frequency of their occurrence in total.

Source: Table 12.1.2: 1 1276.28 study report

7.4.2 Laboratory Findings

No clinically relevant laboratory value was reported by the applicant for studies 1276.13, 1276.14, and 1276.15

Study 1276.28

One subject (101) SGOT value increased from 28 U/L at baseline to 186 U/L ten days later at the end-of –trial examination (reference range 0-50 U/L). SGPT for the same subject was also elevated to 118 U/L at the end of study visit. The applicant reported that bilirubin was within reference range, and that, for this reason, the abnormal liver function tests were not followed up.

7.4.3 Vital Signs

No clinically relevant abnormality in vital signs was reported by the applicant in any of the four phase 1 studies.

7.4.4 Pediatrics and Assessment of Effects on Growth

Not applicable. No pediatric patients were enrolled in this study.

8 Postmarket Experience

Both empagliflozin (Jardiance) and empagliflozin-metformin IR (Synjardy) are FDA approved for the treatment of T2DM. Jardiance was approved on August 1, 2014, and Synjardy was approved on August 28, 2015.

During the review of this application, the applicant submitted a 4 months safety update for this supplement on April 27, 2016. This update report is based on the post-marketing safety data and medical literature data for Synjardy and Jardiance received between 18 Oct 2015 to 10 Feb 2016.

For the reporting period, only one serious adverse event was reported for Synjardy (diabetic ketoacidosis - DKA, non-fatal), in addition to five non-serious spontaneous reports.

For Jardiance there were a total of 79 serious cases with 129 serious events received in this review period; including 5 fatal case reports.

This information was reviewed during the 915 review for empagliflozin which was completed during this review, covering the time period for the safety update, review dated October 17, 2016.

A few safety issues have been identified in the postmarketing setting with the empagliflozin component of the FDC tablet, and I will discuss them below.

Diabetic ketoacidosis

In December 2015, the FDA issued a Drug Safety Communication[1] (DSC) informing that labelling for SGLT2 inhibitors had been updated to warn about the risks of ketoacidosis. The FDA requested that BI conduct a 5-year enhanced pharmacovigilance study of ketoacidosis in patients treated with empagliflozin as a post-marketing requirement, and additionally requested an update relevant study documents (IB, study protocol, informed consent) on the topic of ketoacidosis.

Urosepsis

In December 2015, the FDA issued a Drug Safety Communication[2] informing that labelling for SGLT2 inhibitors had been updated to warn about the risk of urosepsis.

[1] http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm
[2] http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm475553.htm

Stroke and thromboembolic events

In correspondence dated August 20, 2015, FDA notified the applicant that a new DARRTS Tracked Safety Issue (TSI) had been created for SGLT-2 inhibitors regarding stroke and thromboembolic events on June 18, 2015, which includes BI marketed products jardiance and Glixambi (and as of August 26, 2015, Synjardy). Review of the EMPA-REG data revealed a non-statistically significant imbalance not favoring empagliflozin was seen for stroke. Other thromboembolic events (not including stroke) did not appear to be associated with empagliflozin treatment in the EMPA-REG study. A postmarketing analysis of spontaneous reports of embolic and thromboembolic events performed by the drug manufacturer in the PBRER covering the period between October 2015 and April 2016 provided limited information: 9 patients were reported with a cerebrovascular event, and two with transient ischemic attack in the time period between drug approval and April 2016. Deep vein thrombosis was reported in three cases, two with accompanying pulmonary embolism.

Acute kidney injury

On January 4, 2016, the FDA notified the applicant of a tracked safety issue (TSI) for sodium-glucose cotransporter-2 (SGLT-2) inhibitors regarding acute kidney injury (AKI). In the PBRER for Jardiance covering the time period between October 2015 and April 2016, the applicant reported 44 cases of renal impairment with 46 relevant events (including 27 SAEs). One fatal event of renal failure was reported in a patient with a fatal outcome in the context of an event of DKA. For most events, the timing of the event was not reported. For the 15 events where timing was reported, five events occurred in the first week of treatment, and 12 in the first month. The interpretation of postmarketing reports is limited by missing information; however, it appears to support the clinical trial data that suggests an increase in the risk of AKI at least early following treatment start.

Bone fractures

A Warning & Precautions statement describing an increased risk of bone fracture was added to the canagliflozin label as part of a supplement approved on September 10, 2015; a Drug Safety Communication on this topic was also issued on that same date. In the reporting period from drug approval to April 2016, the applicant only reports two spontaneous cases of bone fractures with empagliflozin. One occurred in a 60-year-old female who experienced a facial bone fracture following a fall. The second one was a report of humeral fracture lacking additional information.

Amputations

A potential signal for lower extremity amputations was identified from interim safety results from the ongoing canagliflozin CVOT (canagliflozin). A DSC[3] on this topic was issued on May 18, 2016. The data from the available PADERs and PBRERs for the reporting period did not provide any information regarding amputations.

Acute pancreatitis

Review of the available PBRERs for Jardiance between drug approval and April 2016 revealed 16 postmarketing spontaneous reports of acute pancreatitis, one of which was fatal. Limited information is available regarding confounding factors, but it is notable that pancreatitis incidence is increased in patients with type 2 diabetes compared to the general population.

Malignancy (urinary tract)

The applicant reported two spontaneous postmarketing reports of bladder cancer, both in male patients above the age of 65, with no additional information available at the time of this review. No spontaneous reports of renal cancer were reported.

Drug-induced liver injury

In the reporting period from drug approval to April 2016, the applicant reported 9 spontaneous cases (15 reports), 4 of which were SAEs. Although none were fatal, the applicant identified one fatal case with a nonfatal SAE of jaundice and elevated hepatic enzymes (the cause of death was reported to be metabolic acidosis, although no further information is available).

No new safety signal emerged specifically from review of the 4 months safety update for this NDA. We are continuing to monitor postmarketing safety information with empagliflozin and metformin XR.

9 Advisory Committee

Not applicable.

[3] http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm

10 Appendices

10.1 Labeling Recommendations

Some labeling recommendations are specified throughout the review. Labeling is not yet finalized at this time.

10.2 Financial Disclosures

Covered Clinical Study (Name and/or Number): 1276.15, 1276.28

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 7		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 7		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Not Applicable		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 7		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ Not Applicable	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ Not Applicable	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) Not Applicable		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:	Not Applicable	from applicant)

Overall, I do not feel that this information changes the validity of the study. These studies are typically conducted at applicant sites, with applicant employees as investigators.

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

/s/

ANDREEA O LUNGU
11/29/2016

WILLIAM H CHONG
11/29/2016

JEAN-MARC P GUETTIER
12/02/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208658 | **Applicant: Boehringer Ingelheim Pharmaceuticals Inc** | **Stamp Date: February 10, 2016**

Drug Name: Synjardy XR | **NDA/BLA Type: NDA**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			x	
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			x	The two pivotal studies are bioequivalence single-dose studies, not efficacy studies

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	See comment above
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	See comment above
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	This application is based on bioequivalence studies
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	This application is based on bioequivalence studies
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			(b) (4) [redacted]
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	This application is based on bioequivalence studies

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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

/s/

ANDREEA O LUNGU
04/20/2016

WILLIAM H CHONG
04/20/2016