CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208658Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	*(see electronic signature)*
From	William H. Chong, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208658
Applicant	Boehringer Ingelheim
Date of Submission	February 2, 2016
PDUFA Goal Date	December 9, 2016
Proprietary Name / Established (USAN) names	SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release)
Dosage forms / Strength	Tablet (mg empagliflozin/mg metformin): 5/100, 12.5/100, 25/1000
Proposed Indication(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) (b) (4)
Recommendation:	*Approval, pending agreement on labeling*
Recommended Indication(s)/Population(s) (if applicable)	*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.*

1. Introduction

This new drug application (NDA) is for a fixed combination drug product (FCDP) containing the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin and the biguanide metformin. Both of the components of the propose FCDP are approved to improve glycemic control in patients with diabetes mellitus. Empagliflozin is also available in an FCDP with metformin immediate-release and with linagliptin. Metformin is also available in combination with a range of other antidiabetic drugs.

This Cross-Discipline Team Leader (CDTL) review will discuss the findings and recommendations from the involved review disciplines. No new clinical efficacy studies were conducted specifically to support this NDA. The data submitted to support this NDA come from clinical pharmacology studies and manufacturing data. As such, much of the focus of this review will be on the data in bridging this new combination with previous data.

2. Background

Type 2 diabetes mellitus (T2DM) is a disease of abnormal glucose homeostasis which results in hyperglycemia. It is one of the most prevalent diseases in the United States and is associated with serious complications including cardiovascular disease, renal impairment, and blindness. Glycemic control has been the accepted target for therapies as studies have shown that improved glycemic control can improve clinical outcomes. [1]

Empagliflozin is an SGLT2 inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). By inhibiting glucose reabsorption in the kidney, empagliflozin increases the urinary excretion of glucose and thus reduces plasma glucose levels.

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

[1] UK Prospective Study Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)". Lancet, 1998; 352(9131): 837-853.

gluconeogenesis, and improving peripheral insulin sensitivity leading to increased peripheral glucose uptake and utilization, metformin lowers plasma glucose levels.

An FCDP of empagliflozin and metformin immediate-release is approved (NDA 206111). This NDA is for an FCDP of empagliflozin and metformin extended-release.

No new clinical efficacy studies were conducted to specifically support this NDA. The applicant is relying upon previous data that demonstrated a contribution of each component to the claimed effect (i.e., glycemic control). These clinical studies were previously reviewed as part of NDA 204629 and NDA 206111. The data submitted to support this new NDA come from clinical pharmacology studies and manufacturing information.

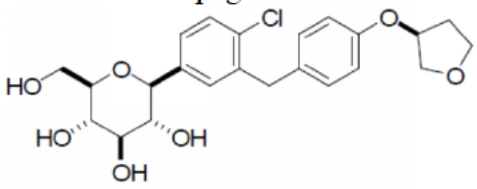
3. CMC/Device

The Office of Pharmaceutical Quality has recommended approval of NDA 208658. For a detailed discussion of the Chemistry, Manufacturing, and Controls information, see the completed Quality reviews.

The two drug substances in this FCDP are empagliflozin and metformin hydrochloride (Figure 1).

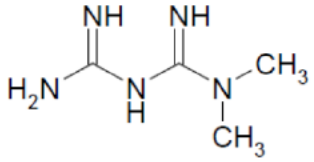
Figure 1: Drug substances

Empagliflozin



Molecular Formula: $C_{23}H_{27}ClO_7$
Molecular Weight: 450.91

Metformin hydrochloride



Molecular Formula: $C_4H_{11}N_5.HCl$
Molecular Weight: 165.6 (b) (4)

Source: Adapted from Dr. Debasis Ghosh's Drug Substance review

To manufacture the FCDP, (b) (4)

(b) (4)

The drug product specifications are adequate based on the release and stability data provided. Degradant limits are within acceptable thresholds. The applicant has proposed a shelf-life of 24 months when stored at room temperature which the OPQ reviewers have granted. The applicant has committed to long-term stability studies (see section 13 of this review for a discussion of postmarketing commitments.

Inspection of the manufacturing facilities has been conducted. The facilities were acceptable.

4. Nonclinical Pharmacology/Toxicology

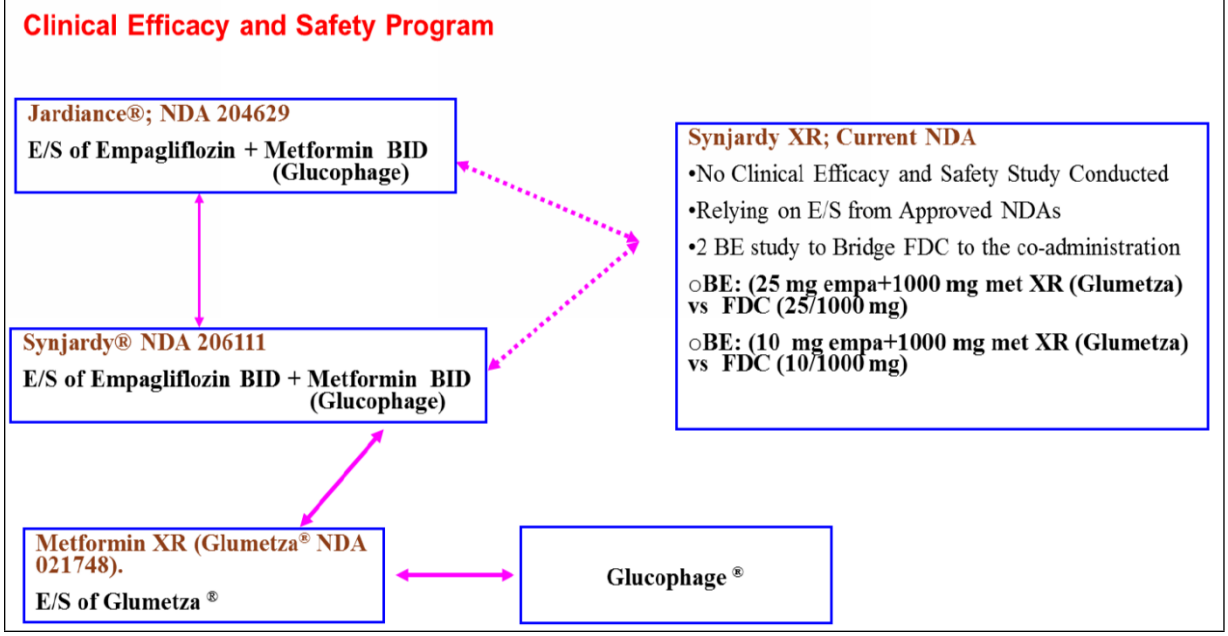
The nonclinical reviewer has recommended approval of this NDA. No nonclinical data were submitted in support of this NDA. Relevant nonclinical studies were reviewed previously (see Dr. David Carlson's reviews in NDA 208026 [submitted May 4, 2016] and NDA 201281 [submitted October 4, 2011], and Dr. Mukesh Summan's review in NDA 206111 [submitted April 15, 2015]).

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology has recommended approval of this NDA.

Two clinical pharmacology studies were conducted to bridge the existing clinical efficacy and safety data to this NDA. The aim of these studies was to demonstrate bioequivalence of the FCDP when compared to co-administration of the individual components (i.e., empagliflozin and metformin hydrochloride extended-release). The applicant's approach to bridging is illustrated in Figure 4 of Dr. Ritesh Jain's clinical pharmacology review (excerpted below).

Figure 4: Schematic Summary of Pivotal Bridging Information Supporting Synjardy® XR

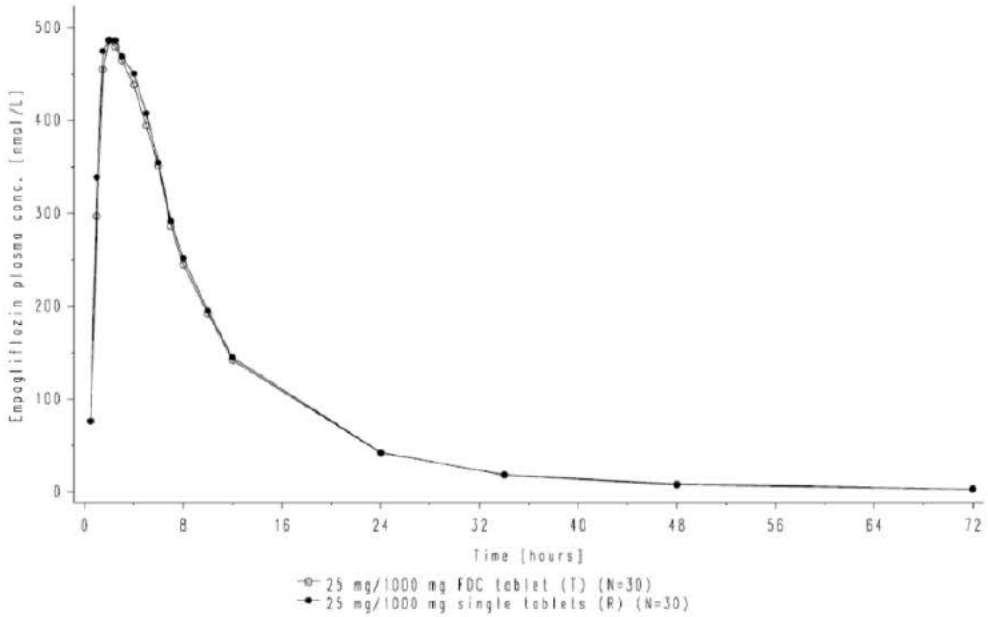


Both studies were 2-way crossover studies. Only two dose combinations were studied (i.e., empagliflozin 10 mg + metformin hydrochloride extended-release 1000 mg in study 1276.28; empagliflozin 25 mg + metformin hydrochloride extended-release 1000 mg in study 1276.15). A biowaiver was requested and granted for other strengths based on the same amount of metformin in all proposed dosage strengths and proportionally similar empagliflozin strengths, demonstration of bioequivalence with the highest strength and a middle strength which also brackets a third strength, and similar dissolution profiles for all proposed dosage strengths.

The results of these two studies showed that the pharmacokinetic profile following administration of the FCDP is comparable to that seen following co-administration of the components (see Figures 5 and 6 of Dr. Jain's clinical pharmacology review, excerpted below).

Figure 5: Plasma concentration time profile following oral administration of 25 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or co-administration of empagliflozin and metformin Tablets (R) under fed condition in Study 1276.15. A) Plasma Concentration Time Profile of Empagliflozin (upper graph) B) Plasma Concentration Time Profile of Metformin (lower graph)

A)



B)

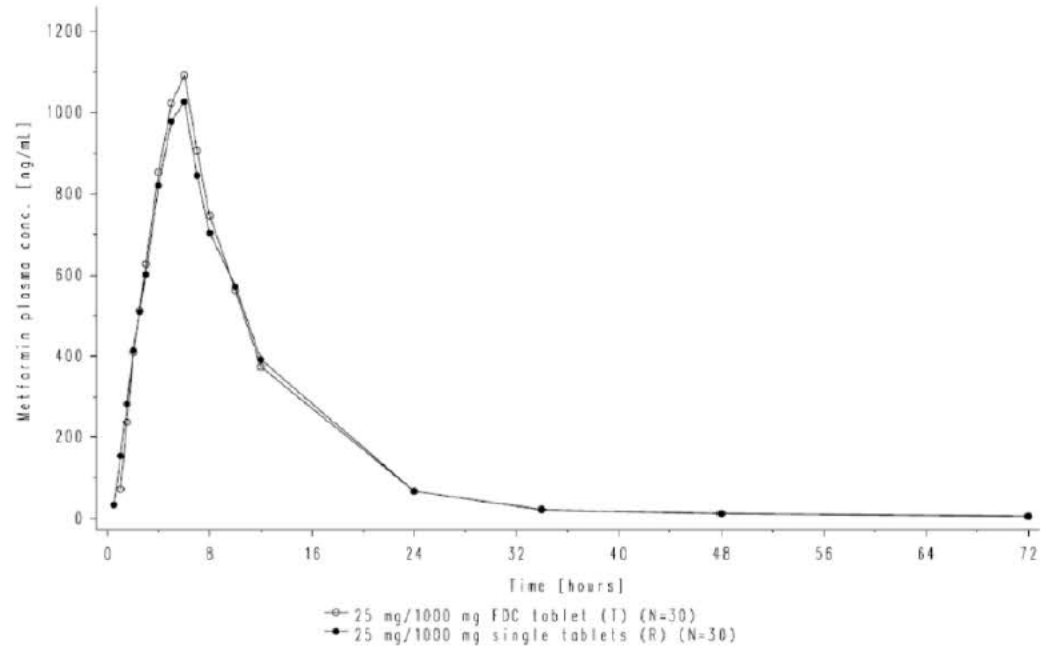
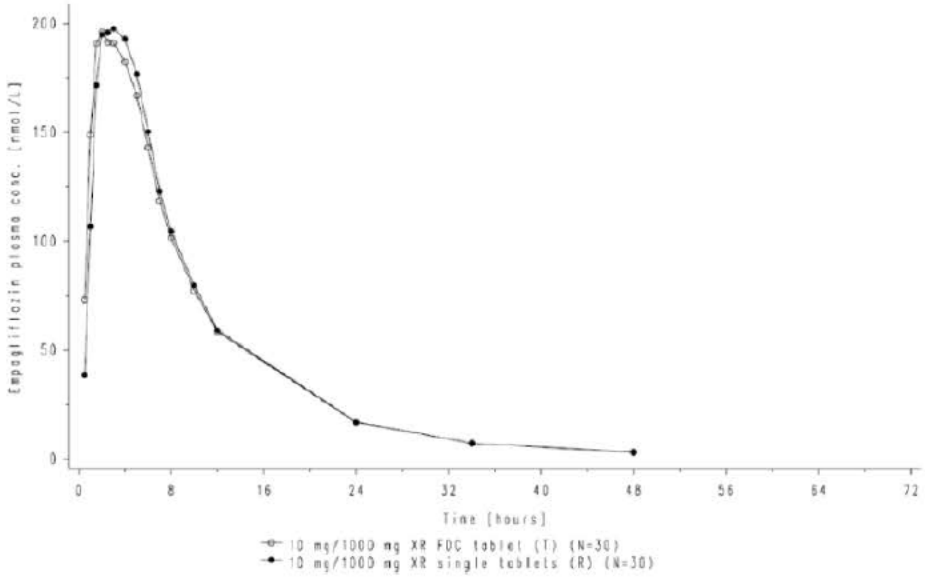
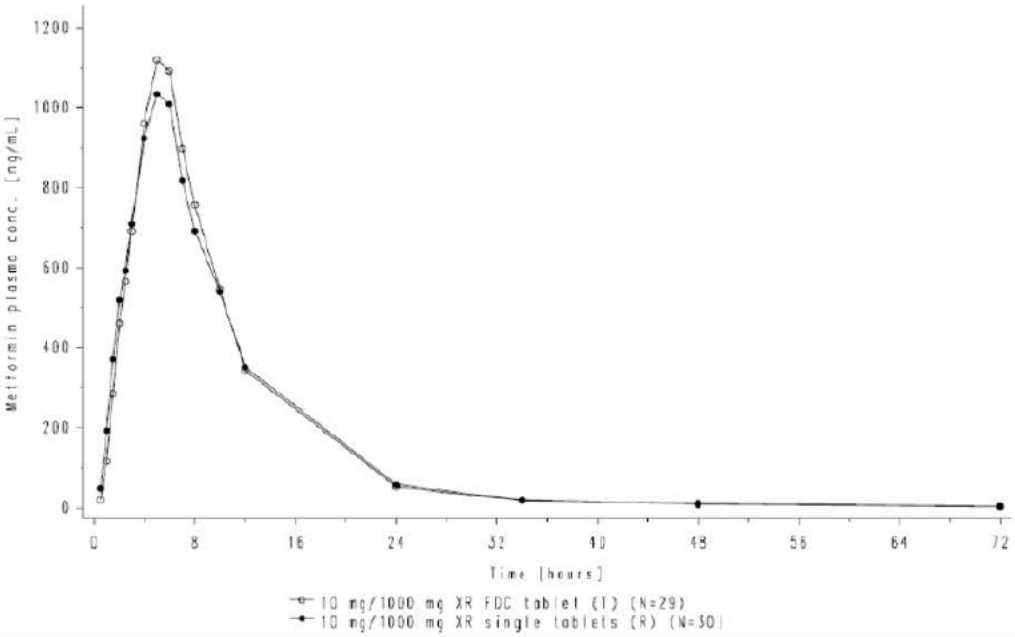


Figure 6: Plasma concentration time profile following oral administration of 10 mg empagliflozin and 1000 mg metformin XR either as FDC (T) or co-administration of empagliflozin and metformin Tablets (R) under fed condition in Study 1276.28. A) Plasma Concentration Time Profile of Empagliflozin (upper graph) B) Plasma Concentration Time Profile of Metformin (lower graph)

A)



B)



No drug-drug interaction studies were performed in support of the FCDP. Studies conducted in support of NDA 204629 did not demonstrate a drug-drug interaction between empagliflozin and metformin.

6. Clinical Microbiology

Not applicable.

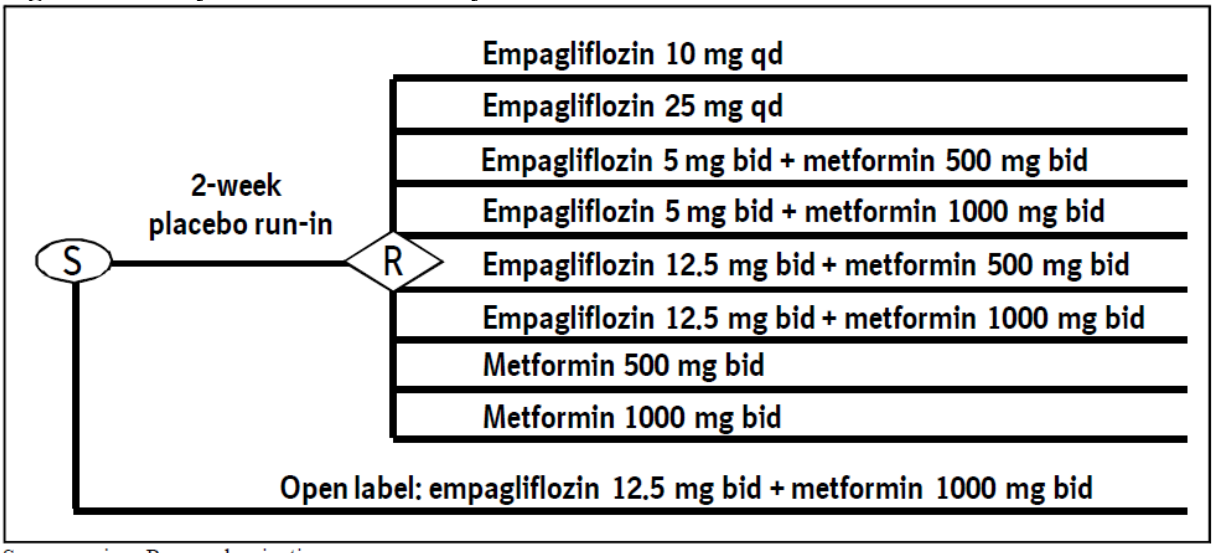
7. Clinical/Statistical- Efficacy

The clinical and statistical reviewers recommend approval of the FCDP.

No new studies were conducted to support the FCDP NDA. The studies that support the FCDP have been previously reviewed under NDA 204629 and NDA 206111. For detailed discussion of the efficacy results, see Dr. Shuxian Sinks review under NDA 206111 and NDA 204629, and Dr. Dongmei Li's review under NDA 204629.

In brief, clinical studies have shown a contribution of each component to the glycemic lowering effect of the FCDP. Additionally, studies have shown a contribution of empagliflozin when added to patients inadequately controlled on metformin (with or without other antidiabetic drugs). The most relevant study to support the indication is study 1276.1. This study was designed to compare the effect of using empagliflozin or metformin individually with the effect of starting empagliflozin and metformin at the same time (Figure 2).

Figure 2: Study schematic for study 1276.1



S = screening, R = randomization
Source: Excerpted from Figure 3.1: 1 from v1.0 (dated April 30, 2012) of the study protocol for study 1276.1

As noted in Dr. Sink's review, use of both components provides a greater reduction in HbA1c compared to use of one of the components alone (see Table 5 of Dr. Sinks statistical review from NDA 206111 and NDA 204629 submitted on February 12, 2016, excerpted below).

Table 5 HbA1c (%) change from baseline ANOVA results at Week 24 –TS (OC-IR) (FDA's Results)

	LS Mean (SE)	Comparison vs E25 QD (95% CI) P-value	Comparison vs M1000 BID (95% CI) P-value	Comparison vs M500 BID (95% CI) P-value	Comparison vs E10 QD (95% CI) P-value
Combination					
E12.5+M1000 BID (n=170)	-1.77 (0.14)	-0.79 (-1.04, -0.54) <0.0001	-0.38 (-0.63, -0.13) <0.0001		
E12.5+M500 BID (n=170)	-1.44 (0.14)	-0.45 (-0.71, -0.20) 0.0004		-0.54 (-0.79, -0.29) <0.0001	
E5+M1000 BID (n=171)	-1.69 (0.14)		-0.30 (-0.55, -0.05) 0.0203		-0.63 (-0.88, -0.38) <0.0001
E5+M500 BID (n=169)	-1.60 (0.14)			-0.70 (-0.95, -0.45) <0.0001	-0.53 (-0.78, -0.29) <0.0001
	LS Mean (SE)		**Comparison vs M1000 BID (95% CI) P-value***		
Monotherapy					
E25 QD (n=167)	-0.99 (0.14)		0.41 (0.16, 0.66) 0.6471		
E10 QD (n=172)	-1.06 (0.14)		0.33 (0.08,0.58) 0.8910		
M1000 BID (n=170)	-1.40 (0.14)				
M500 BID (n=171)	-0.90 (0.14)				

Note: Model includes baseline HbA1c as linear covariate and baseline eGFR, region, treatment as fixed effects. Missing data are imputed using multiple imputation and all observed cases of change from baseline at week 24 weeks are treated as non-missing.
*non-inferiority test at alpha=0.025 with the specified margin of 0.35%

(b) (4)

8. Safety

The clinical reviewer recommends approval of the FCDP.

The only new clinical studies conducted to specifically support this NDA were clinical pharmacology studies. The safety of combining empagliflozin and metformin has been previously reviewed under NDA 206111 (see my review under NDA 206111 submitted on June 4, 2015 and Dr. Andreea Lungu's review under NDA 206111 submitted on June 1, 2016). The observed adverse reaction profile is consistent with what would be seen when combining the two drug products. No evidence of amplified safety concerns was seen.

9. Advisory Committee Meeting

Not applicable. No Advisory Committee meeting was held to discuss this NDA.

10. Pediatrics

For the glycemic control indications, the applicant has requested a waiver for pediatric studies in children with type 2 diabetes mellitus < 10 years of age as a study is highly impractical due to the very small number of patients. I agree with this request, and the request was discussed with the Pediatric Review Committee (PeRC) on September 28, 2016. The PeRC also agreed.

For the glycemic control indication, the applicant has requested a deferral of studies in children with type 2 diabetes mellitus ages 10 to 17 (inclusive). I agree with this request, and the request was discussed with the PeRC on September 28, 2016. The PeRC also agreed. The design of the planned study to fulfill the Pediatric Research Equity Act (PREA) is currently under discussion with the Division. The planned study is intended to fulfill the PREA requirements for the empagliflozin drug product. The PREA requirements for the empagliflozin and metformin hydrochloride combination drug products will be satisfied by this study as well.

11. Other Relevant Regulatory Issues

Financial disclosures for the clinical pharmacology studies are discussed in Dr. Lungu's review. While investigators for these studies are applicant employees, I am not concerned that this could have biased the results. The assessments are based on objective measurements of drug concentrations. This is also typical of these kinds of studies.

Financial disclosures for the clinical studies that support the glycemic control indication are discussed in my review under NDA 206111 submitted on June 4, 2015 and in Dr. Andreea Lungu's review under NDA 206111 submitted on June 1, 2016.

12. Labeling

The proposed proprietary name of SYNJARDY XR was reviewed by the Division of Medication Error Prevention and Analysis and found to be acceptable.

(b) (4)

The language for the proposed glycemic control indication should be changed to read "when treatment with both empagliflozin and metformin is appropriate". The results of study 1276.1 support this indication and it is the indication in the current empagliflozin and metformin hydrochloride immediate-release FCDP.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of this NDA.

- Risk Benefit Assessment

The data previously reviewed in support of NDA 206111 demonstrated that combining empagliflozin and metformin (b) (4)

(b) (4)

The risks associated with combination therapy are consistent with the current labeling of the individual products and with the approved FCDP (i.e., NDA 206111 [SYNJARDY]). In considering the risk-benefit of this FCDP, it is no different than the SYNJARDY drug product which was concluded to be favorable.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I do not recommend a Risk Evaluation and Management Strategy.

- Recommendation for other Postmarketing Requirements and Commitments

Post-Approval Stability Commitments
The applicant has provided a post-approval stability testing protocol and has committed:

1) To continue long term stability studies for the primary stability batches
2) To place the first production batches of the drug product manufactured using empagliflozin drug substance synthesized at the alternate API supplier (b) (4) on stability testing.
3) To place the first production batches of the drug product manufactured using empagliflozin drug substance synthesized at (b) (4) on long-term stability conditions.
4) To place the first production batches of the drug product manufactured using empagliflozin drug substance (b) (4) on stability.
5) To test drug product each year of commercial production; provide the results from the stability testing to the FDA.
6) To withdraw from the market any batch found to fall outside the approved specifications of the drug product.

PREA Postmarketing Requirements:
Studies intended to fulfill the PREA requirements are currently under discussion. This includes a clinical efficacy and safety study. The design of this study is under discussion, and this study is intended to be applicable to NDA 204629, NDA 206111, and to this NDA.

- Recommended Comments to Applicant

None.

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/s/

WILLIAM H CHONG
12/01/2016

JEAN-MARC P GUETTIER
12/02/2016

I concur with recommendations to approve this NDA. Dr. Chong's memorandum serves as the summary basis for approval of this application.