CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206111Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	August 18, 2015
From	William H. Chong, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA-206111 Resubmission of NDA
Applicant	Boehringer Ingelheim
Date of Submission	July 2, 2015
PDUFA Goal Date	September 2, 2015
Proprietary Name / Established (USAN) names	SYNJARDY (empagliflozin/metformin tablet)
Dosage forms / Strength	Oral tablet (empagliflozin/metformin: 5mg/500mg, 5mg/1000 mg, 12.5mg/500mg, and 12.5mg/1000mg)
Proposed Indication(s)	1. Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin
Recommended:	*Approval*

1. Introduction

The proposed New Drug Application (NDA) product is a fixed combination drug product consisting of empagliflozin (a sodium glucose cotransporter-2 [SGLT2] inhibitor) and metformin (a biguanide) for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. The NDA was originally submitted on August 4, 2014. A Complete Response letter was issued on June 4, 2015 outlining the following deficiency and ways to resolve the deficiency:

Deficiency:

We have been unable to reach agreement on the proposed labeling (21 CFR 314.125). Specifically, we have concluded that (b) (4) does not support (b) (4) and that (b) (4) is misleading for the following reasons:

(b) (4)

We view the 52-week efficacy data (b) (4) reliable, robust and as sufficient to inform the safe and effective use of the product in this setting.

Resolution of deficiency

To address this deficiency, you will need to submit labeling which adequately addresses our concern that (b) (4) could be misleading.

This current submission contains the resubmission from the applicant addressing the outlined deficiency.

2. Background

Empagliflozin is a sodium-glucose cotransporter-2 (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 gluconeogenesis, and improving peripheral insulin sensitivity leading to increased peripheral glucose uptake and utilization, metformin lowers plasma glucose levels.

This fixed combination drug product (FCDP) combines these two products into a single tablet.

Safety concerns with SGLT2 inhibitors include:

- Volume depletion/hypotension
- Impairment of renal function
- Genitourinary infections (especially genital mycotic infections)
- Increases in low density lipoprotein cholesterol (LDL-C)
- Hypoglycemia with concomitant insulin or insulin secretagogue therapy

Safety concerns with metformin include:

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

3. CMC/Device

Not applicable. There is no CMC/Device information included in this resubmission. See the previously completed review by Dr. Joseph Leginus.

4. Nonclinical Pharmacology/Toxicology

Not applicable. There is no nonclinical information included in this resubmission. See the previously completed review by Dr. Mukesh Summan for discussion of nonclinical issues.

5. Clinical Pharmacology/Biopharmaceutics

Not applicable. There is no new clinical pharmacology/biopharmaceutics information submitted for review with this resubmission. See the previously completed reviews by Dr.

Suryanarayana Sista and Dr. Kelly Kitchens for discussion of the clinical pharmacology and biopharmaceutics issues.

6. Clinical Microbiology

Not applicable. There is no clinical microbiology information included in this resubmission. See the memorandum from Dr. John Metcalfe for discussion of microbiology issues

7. Clinical/Statistical- Efficacy

The issues with regard to labeling that led to the Complete Response were discussed further (b) (4) Agreement was reached on language (b) (4) The proposed label included in the resubmission for this NDA reflects that agreed upon language.

8. Safety

As part of this resubmission, the applicant has included a safety update. The applicant reports that four clinical studies have been completed since the time of the initial NDA submission, but only two have completed study reports. These are a phase 2 study (study 1245.78) exploring empagliflozin in patients with type 1 diabetes mellitus, and a phase 3 study (study 1276.1) exploring the efficacy and safety of empagliflozin+metformin versus the individual components. The other two completed studies are sequential add-on studies examining the efficacy of combining empagliflozin and linagliptin in a sequential fashion.

The focus of the safety update included in the resubmission is the data from study 1276.1. The applicant's rationale for this is that this is the only study with data relevant to this NDA. I agree with this approach. I also agree with the approach to not pool the results from this study with previous safety data.

Based on the applicant's review of the additional safety data since the initial NDA submission, they report that there has been no change to the safety profile of this FCDP. My review of the included study report is in concurrence with this assessment. Note that study 1276.1 is the subject of an ongoing efficacy supplement submitted to NDA-204629 (empagliflozin) and the safety findings from study 1276.1 will be discussed in greater detail as part of that review.

There is limited additional post-marketing safety data for empagliflozin or for the FCDP, though the applicant acknowledges the current concerns regarding ketoacidosis with use of SGLT2 inhibitors. This is a tracked safety issue and is currently being considered in detail by the Agency.

I have not identified new safety data which would warrant not approving the NDA.

9. Advisory Committee Meeting

Not applicable. No advisory committee meeting was held to discuss this resubmission.

10. Pediatrics

Not applicable. No pediatrics information is included in this resubmission.

11. Other Relevant Regulatory Issues

Though this resubmission was received after the June 30, 2015 date associated with the Pregnancy and Lactation Labeling Rule (PLLR) going to effect, it was determined that this resubmission would not have to comply with PLLR formatting of the label.

12. Labeling

The proposed proprietary name (SYNJARDY) was deemed acceptable during the initial review. No promotional or safety concerns were identified. The proposed name was considered again during this resubmission and was again deemed acceptable. Labeling discussions to address the deficiency outlined in the Complete Response letter were completed as part of an efficacy supplement submitted to NDA-204629 (JARDIANCE [empagliflozin]). Additional minor changes were proposed by the applicant. (b) (4) These are acceptable.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

During the initial NDA review cycle, it was concluded that the FCDP of empagliflozin + metformin was efficacious and that the safety data in support of the combination did not suggest any new safety concerns that are not already known for the individual components. In this resubmission, there is no new information which would alter this conclusion. Thus, I continue to believe that the benefit of additional glycemic control adequately justifies the risks associated with use in adults with T2DM.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategy is recommended for this NDA.

- Recommendation for other Postmarketing Requirements and Commitments

No new postmarketing requirements are recommended for this NDA. The pediatric studies required for empagliflozin should be referenced in the approval letter and should be satisfactory to inform the use of this FCDP in pediatrics once completed.

- Recommended Comments to Applicant

No additional comments are recommended at this time.

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/s/

WILLIAM H CHONG
08/18/2015

JEAN-MARC P GUETTIER
08/24/2015

The applicant has addressed the deficiency in the CR letter. I concur with Dr. Chong's assessment and recommend approval. See previous reviews in DARRTs.