CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	December 31, 2014
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK)
Team Leader:	Naomi Redd, Pharm.D, Acting Team Leader DRISK
Division Director	Cynthia LaCivita, Pharm.D, Acting Director DRISK
Subject:	Evaluation of need for a REMS
Drug Name(s):	Empagliflozin-Linagliptin (Glyxambi)
Therapeutic Class:	Sodium-dependent glucose co-transporter-2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor fixed dose combination product
Dosage and Route:	10 mg empagliflozin/5 mg linagliptin and 25 mg empagliflozin/5 mg linagliptin tablet once daily/oral
Application Type/Number:	NDA 206073
Submission Number:	Orig-1, 0000
Applicant/sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2014-524 and 2014-527

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a risk evaluation and mitigation strategy (REMS) is necessary for empagliflozin-linagliptin fixed-dose combination product (NDA 206073, 505 (b)(1) submission received by FDA on January 30, 2014). Empagliflozin is a sodium-dependent glucose co-transporter-2 (SGLT2) inhibitor and linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. Both products were developed by Boehringer Ingelheim Pharmaceuticals.

Boehringer Ingelheim Pharmaceuticals is seeking approval for empagliflozin-linagliptin fixed-dose combination product as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when both empagliflozin and linagliptin are appropriate.

1.1 Background

The empagliflozin-linagliptin fixed-dose combination product is formulated as a tablet for oral administration and comes in two dosage strengths: 10 mg empagliflozin/5 mg linagliptin and 25 mg empagliflozin/5 mg linagliptin. Proprietary name for empagliflozin-linagliptin fixed-dose combination product, Glyxambi®, was approved by FDA on May 9, 2014. The PDUFA goal date for this application is on January 30, 2015.

Linagliptin (Tradjenta, NDA 201280) was approved by FDA on May 2, 2011 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The linagliptin label includes warnings for pancreatitis, hypoglycemia (when used in combination with insulin or insulin secretagogues), and hypersensitivity reactions. Linagliptin in combination with metformin (Jentadueto, NDA 201281) was approved by FDA on January 30, 2012 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate; it carries a boxed warning for lactic acidosis as does the metformin label.

Empagliflozin (Jardiance, NDA 204629) was approved by FDA on August 1, 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Please refer to DRISK reviews dated November 12, 2013 and July 28, 2014 including an evaluation of the need for a REMS for empagliflozin. The empagliflozin label includes warnings for hypotension, renal impairment, hypoglycemia (when used in combination with insulin or insulin secretagogues), genital mycotic infections, urinary tract infections, and for increases in low-density lipoprotein cholesterol.

Tradjenta, Jentadueto, and Jardiance do not have risk evaluation and mitigation strategy (REMS). Boehringer Ingelheim Pharmaceuticals did not include a REMS or risk management plan in this submission.

1.2 Regulatory History

Following is the regulatory history, in pertinent part:

- **January 30, 2014:** Application received
- **March 30, 2014:** Application filing date

- **June 24, 2014:** Internal Mid-Cycle meeting. FDA communicated to the sponsor the apparent lack of additional efficacy of the empagliflozin and linagliptin 25 mg/5 mg combination over empagliflozin 25 mg alone in the treatment naïve study population.
- **July 8, 2014:** External Mid-Cycle meeting
- **October 15, 2014:** Internal Late Cycle meeting
- **October 30, 2014:** External Late Cycle meeting
- **December 10, 2014:** Wrap-up meeting
- **January 30, 2015:** PDUFA goal date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Empagliflozin, DRISK Review, dated November 12, 2013 and July 28, 2014.
- Empagliflozin-linagliptin, submission cover letter, January 30, 2014.
- Empagliflozin-linagliptin proposed label, January 30, 2014.
- Empagliflozin-linagliptin Introduction-Summary, January 30, 2014.
- Empagliflozin-linagliptin mid-cycle communication, July 10, 2014.

3 RESULTS OF REVIEW

3.1 CLINICAL DEVELOPMENT PROGRAM

The clinical development program included two phase I trials and one pivotal phase III trial (Study 1275.1). The phase III trial included a total of 1363 patients with type 2 diabetes mellitus with and without a background of metformin randomized and followed for up to 52 weeks. This trial evaluated the efficacy and safety of two doses of empagliflozin/linagliptin combination (empagliflozin10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg) compared to the individual components. The primary endpoint was change in HbA1c after 24 weeks of treatment.

In patients with background treatment with metformin, the empagliflozin/linagliptin combination (both doses) showed greater reduction in HbA1c when compared to the individual components (reached statistical significance for all comparisons). However, in the treatment naïve population, the empagliflozin 25 mg/linagliptin 5 mg was not statistically significantly better than empagliflozin 25 mg alone decreasing HbA1c.

3.2 SAFETY CONCERNS

No new safety concerns were identified – the observed safety profile is consistent with that of each individual product in the combination.

4 CONCLUSIONS AND RECOMMENDATIONS

The safety profile of the empagliflozin-linagliptin fixed-dose combination product identified by the clinical development program is consistent with the profiles of each individual product and can be communicated though labeling. DRISK does not recommend a REMS at this time.

If new safety concerns emerge during the review of this application, please include DRISK in any discussion regarding selection of a risk management approach.

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/s/

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12/31/2014

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01/02/2015
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