

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204629Orig1s000

**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: July 28, 2014

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Doris Auth, Pharm.D, Team Leader
DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director
DRISK

Subject: Evaluation of need for a REMS

Drug Name(s): Empagliflozin (Jardiance[®])

Therapeutic Class: Sodium-dependent glucose co-transporter-2 (SGLT2)
inhibitor

Dosage and Route: 10 mg, 25 mg tablet once daily/oral

Application Type/Number: NDA 204629

Submission Number: Resubmission, June 3, 2014 (0032)

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2013-619 and 2013-656

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that should not be released to the public**

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 (NDA 204629).

Boehringer Ingelheim Pharmaceuticals, Inc. is seeking approval for empagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). DRISK reviewed the original application for empagliflozin submitted to FDA on March 5, 2013 and determined that a REMS was not required to manage the serious risks associated to empagliflozin (e.g., hypoglycemia, volume depletion, and genital infections). See DRISK review dated November 12, 2013.¹

The original application received a complete response (CR) letter on March 4, 2014. The CR letter cited deficiencies identified during inspection of a facility in Germany (FEI 3002806556). On May 28, 2014, FDA Division of International Drug Quality notified the Applicant that the facility (FEI 3002806556) was reclassified as acceptable. A class 1 resubmission for empagliflozin was received by FDA on June 3, 2014 including the Applicant's response to the deficiency identified in the CR letter, proposed draft labeling, and a safety update.

Boehringer Ingelheim Pharmaceuticals did not include a REMS or risk management plan in this resubmission.

Proprietary name, Jardiance[®], was approved by FDA on June 18, 2014.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Empagliflozin, DRISK Review, dated November 12, 2013.
- Empagliflozin, resubmission cover letter, June 3, 2014.
- Empagliflozin proposed label, June 3, 2014.
- Empagliflozin safety update, June 3, 2014.

3 RESULTS OF REVIEW

Data included in the June 3, 2014 submission do not change the safety profile characterized for empagliflozin during the initial review cycle.

4 CONCLUSIONS AND RECOMMENDATIONS

The data included in this class 1 resubmission does not change the known safety profile of empagliflozin. DRISK's original recommendation that a REMS is not required to manage the serious risks associated to empagliflozin remains unchanged.

Please contact DRISK if you have any questions.

¹ Amarilyn Vega, MD, MPH: DRISK Review for Empagliflozin (NDA 204629), dated November 12, 2013.

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/s/

AMARILYS VEGA
07/28/2014

CYNTHIA L LACIVITA
07/28/2014
Concur

**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**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: November 12, 2013

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D, Team Leader
DRISK

Division Director: Claudia Manzo, Pharm.D, Director
DRISK

Drug Name(s): Empagliflozin (proposed Jardiance)

Therapeutic Class: Sodium-dependent glucose co-transporter-2 (SGLT2)
inhibitor

Dosage and Route: 25 mg tablet once daily/oral

Application Type/Number: NDA 204629

Submission Number: ORIG-1, March 5, 2013

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2013-619 and 2013-656

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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 (NDA 204629, proposed tradename Jardiance[®]). Boehringer Ingelheim Pharmaceuticals, Inc. is seeking approval for empagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Boehringer Ingelheim Pharmaceuticals, Inc. did not submit a Risk Evaluation and Mitigation Strategy (REMS) but did include a risk management plan (RMP) with this application.

1.1 BACKGROUND

*Empagliflozin.*¹ Empagliflozin is a reversible, potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is highly expressed in the kidney (proximal tubules) where it is responsible for 90% of glucose reabsorption from the glomerular filtrate back into the circulation. Inhibition of SGLT2 reduces renal reabsorption of glucose resulting in reduction of glucose in blood. SGLT2 expression in other tissues is negligible. Empagliflozin also has a 5000-fold selectivity over human SGLT1, responsible for glucose absorption in the gut.

Empagliflozin is formulated as 10 and 25 mg tablets for oral administration; both formulations were evaluated during drug development. The Applicant is recommending use of the 25 mg tablet once daily regimen only because they believe the totality of the data demonstrated slightly but consistently better efficacy of the 25 mg dose when compared to the 10 mg dose regimen.

As of the time of this review, empagliflozin has not been commercialized in any country.

Other SGLT2 inhibitors. Currently, canagliflozin (Invokana[®]) is the only FDA-approved SGLT2 inhibitor (approved on March 29, 2013). Canagliflozin is contraindicated in patients with severe renal impairment (eGFR < 30mL/min/1.73m²), end-stage renal disease or patients on dialysis. Key safety concerns listed in the Warnings and Precautions sections of the canagliflozin label include the following:

- Hypotension
- Impairment of renal function
- Hyperkalemia
- Hypoglycemia (with concomitant use of insulin and insulin secretagogues)
- Genital mycotic infections
- Hypersensitivity reactions
- Increased in LDL-cholesterol

¹ Clinical Overview, dated February 5, 2013.

Canagliflozin was approved without a REMS; product label includes a Medication Guide. Other SGLT2 inhibitors under clinical development include dapagliflozin, (b) (4) (b) (4) (b) (4) 2,3 .

See Appendix 1 for a side-by-side comparison of labeling for canagliflozin, empagliflozin, and dapagliflozin.

1.2 REGULATORY HISTORY

Following is the regulatory history, in pertinent part.

April 10, 2008: Boehringer Ingelheim submitted the Investigational New Drug Application (IND 102145) for the development of empagliflozin for the treatment of T2DM.

March 5, 2013: NDA 204629 submitted to FDA for review.

July 25, 2013: A communication from the Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology to the Applicant regarding proposed proprietary name, indicated that the proposed proprietary name Jardiance received conditional acceptance and will be re-reviewed 90 days prior to the approval of the NDA.

September 5, 2013: Mid-cycle communication. Key safety concerns included potential liver toxicity (elevation of transaminases and multiple Hy's Law cases) and neoplasms (a signal for lung cancer and melanoma).

Important upcoming dates:

January 13, 2014: Wrap up meeting

March 5, 2014: PDUFA date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Clinical Overview, dated February 5, 2013
- Nonclinical Overview, dated January 9, 2013
- Summary of Clinical Efficacy, dated February 7, 2013
- Summary of Clinical Safety, dated February 7, 2013
- Risk Management Plan, dated February 1, 2013
- Draft Empagliflozin label, October 11, 2013
- Mukesh Summan, PhD, Pharmacology/Toxicology Review, dated November 5, 2013
- William Chong, MD, Clinical Review, November 5, 2013

(b) (4)

3 RESULTS OF REVIEW

At the time this review was completed, FDA's review of the dossier submitted by the Applicant in support of the efficacy and safety of empagliflozin was still ongoing.

3.1 OVERVIEW OF CLINICAL PROGRAM⁴

The clinical development program for empagliflozin consisted of 48 clinical trials including 30 Phase I trials, 5 dose-finding Phase II trials, and 13 Phase IIb/III trials. Empagliflozin was evaluated as monotherapy and in combination with metformin, glimepiride, pioglitazone, insulin and dipeptidyl-peptidase 4 (DPP-4) inhibitors (sitagliptin). Clinical trials included 13767 patients; 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 for at least 52 weeks and 1486 for at least 76 weeks. All cardiovascular events were independently adjudicated and evaluated in a prospective meta-analysis.

3.1.1 Nonclinical Findings^{5,6}

The Applicant claims that empagliflozin has no effects on fertility and early embryonic development in rats and was not teratogenic in rats or rabbits.

Reproductive toxicology studies in other SGLT2 inhibitors showed morphological effects in the kidneys of juvenile rats (i.e., renal pelvic and tubular dilatation) and are considered a class effect.⁷ Juvenile toxicity studies in the rat were not conducted by the sponsor for empagliflozin; however, animal studies demonstrated that empagliflozin was present in fetal tissues and in maternal milk. This is considered sufficient evidence of potential human risk.

3.1.2 Efficacy⁸

The Applicant's clinical development program demonstrated that empagliflozin is effective in reducing glycosylated hemoglobin (HbA1c) when used as monotherapy and as add-on to other antidiabetic regimens (including metformin, metformin + sulfonylureas, pioglitazone, and basal insulin). The efficacy of empagliflozin was evaluated in a pool of 11250 patients: 3021 patients were randomized to empagliflozin 10 mg, 3994 patients were randomized to empagliflozin 25 mg, 3081 patients were randomized to receive placebo and 1154 patients were randomized to an active comparator. Patients with severe renal disease were excluded. The primary study endpoint is change from baseline in glycosylated hemoglobin (HbA_{1c}). Pivotal trials demonstrated superiority of both doses of empagliflozin to placebo. The adjusted mean difference in HbA1c from placebo ranged between -0.48% and -0.73% for empagliflozin 10 mg and between -0.59% and -0.84% for empagliflozin 25 mg after 24 weeks of

⁴ Clinical Overview, dated February 5, 2013

⁵ Nonclinical Overview, dated January 9, 2013.

⁶ Mukesh Summan, PhD, Pharmacology/Toxicology Review, dated November 5, 2013.

⁷ Canagliflozin is Pregnancy Category C.

⁸ Summary of Clinical Efficacy, dated February 7, 2013.

treatment; the decrease in HbA_{1c} was sustained for at least 52 weeks. In addition, empagliflozin 25 mg demonstrated non-inferiority to glimepiride (1 mg to 4 mg). Observed changes in fasting plasma glucose and in postprandial glucose support the changes observed in HbA_{1c}. There was reduced efficacy of empagliflozin in patients ≥ 75 years old and in patients with severe renal impairment.

Empagliflozin also demonstrated significant and clinically meaningful reductions in HbA_{1c} when compared to placebo in subpopulations of diabetic patients who also had hypertension, renal impairment, or increased cardiovascular risk and in patients who were already receiving insulin therapy. Furthermore, when compared to placebo, treatment with empagliflozin also resulted in reduction in body weight and systolic blood pressure.

3.1.3 Safety Concerns^{9,10}

The evaluation of safety consisted of analyses of several datasets, each representing a particular stratum of safety data. The risk management plan submitted by the Applicant is based on two safety analysis sets (SAF):

- SAF-10: randomized, double-blind, placebo-controlled studies. Included a total of 995 patients receiving placebo and 977 patients treated with empagliflozin 25 mg.
- SAF-11: all studies in patients with T2DM, cumulative data for treatment groups. Included a total of 3522 patients receiving placebo and 4602 patients treated with empagliflozin 25 mg.

The analysis of safety data identified the following risks: genitourinary infections and volume depletion (patients >75 years). The frequency of urinary tract infections was similar between patients treated with empagliflozin 25 mg (7.6%) and placebo (7.6%). Urinary tract infection occurred more frequently in female patients (15.5% empagliflozin 25 mg, 12.5% placebo) than in male patients (1.6% empagliflozin 25 mg, 3.1% for placebo). Elderly patients had a higher frequency of urinary tract infections than younger patients. An increase in the frequency of volume depletion was observed in association with increases in age for both placebo (<50 years 0.9%, 50 to <65 years 1.0%, 65 to <75 years 2.1% for ≥ 75 years 2.1%) and empagliflozin 25 mg (<50 years 0.7%, 50 to <65 years 1.0%, 65 to <75 years 2.1%, and ≥ 75 years 4.4%). Decreases in renal function were also observed with empagliflozin, particularly when used to treat older patients (≥ 75 years) or patients with moderate renal impairment at baseline. The Applicant proposed managing these risks through labeling and pharmacovigilance; the risks of volume depletion and hypoglycemia to be included in the Warnings and Precautions section.

Additional safety concerns included potential liver toxicity, risk for malignancies, hypoglycemia, and cardiovascular safety. There were no imbalances in the number of liver-related adverse events reported in clinical trials although more patients in the empagliflozin group met biochemical criteria for Hy's Law; however, upon further analysis, all cases had other possible etiologies. There was an imbalance in lung and

⁹ Risk Management Plan, dated February 1, 2013.

¹⁰ Draft Empagliflozin label, September 12, 2013.

melanoma cases in the empagliflozin group; however most cases had risk factors for cancer. In addition, there is no identified biological mechanism to support the potential association between treatment with empagliflozin and carcinogenicity. An increased incidence of hypoglycemia was observed when empagliflozin was added to other antidiabetic agents. There was no signal of increased cardiovascular risk identified in clinical trials. A meta-analysis of major adverse cardiovascular events, which includes interim data from the ongoing cardiovascular safety study, excluded an upper bound of 1.8 for the 95% confidence interval.¹¹

4 CONCLUSIONS AND RECOMMENDATIONS

Empagliflozin's clinical development program demonstrated this drug is effective in the management of T2DM in patients with normal, mild, or moderately impaired renal function. The safety profile of this drug is consistent with that of Invokana (canagliflozin) including the serious risks of hypoglycemia when used concomitantly with other antihyperglycemic agents and the risk of volume depletion.

DRISK determined that a REMS is not required to manage the risks associated to empagliflozin. DRISK concurs with the Division of Metabolism and Endocrinology Products' (DMEP) recommendation to manage the serious risks of hypoglycemia and volume depletion associated to empagliflozin through labeling. Hypoglycemia is a well-known complication of antihyperglycemic therapy and the risk for volume depletion is expected due to empagliflozin's mechanism of action. The anticipated prescriber populations (endocrinologists, internists, and family practitioners) are familiar with the management of patients with T2DM and the risks associated to this disease. Similar risks associated to the use of canagliflozin have been effectively managed through labeling, thus far. The risks for hypoglycemia and volume depletion will be included in the Warning and Precautions section of the label. The potential risk of teratogenicity is considered a class effect. It is likely that empagliflozin will be labeled as Pregnancy Category C, as canagliflozin, the other FDA-approved drug in the class.

¹¹ William Chong, MD, Clinical Review, November 5, 2013.

Appendix 1. Side-by-Side Comparison: Empagliflozin, Canagliflozin, and Dapagliflozin

	DAPAGLIFLOZIN <i>(proposed labeling)</i>	CANAGLIFLOZIN	EMPAGLIFLOZIN <i>(proposed labeling)</i>
General Information			
Trade Name:	(b) (4) <i>(pending final approval)</i>	Invokana	Jardiance <i>(pending final approval)</i>
Sponsor:	Bristol-Myers Squibb and AstraZeneca	Janssen Pharmaceuticals, Inc.	Boehringer Ingelheim Pharmaceuticals
NDA:	202293	204042	204629
Class:	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor
Indication:	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
FDA Approval Date:	Pending	March 29, 2013	Pending
Risk Management of Key Safety Issues			
Boxed Warning:	None	None	None
Warning & Precautions:	<ul style="list-style-type: none"> • Use in patients at risk for volume depletion • Use with medications known to cause hypoglycemia • Use in patients with renal impairment • Pregnancy • Nursing mothers 	<ul style="list-style-type: none"> • Hypotension • Hypoglycemia with concomitant use with insulin and insulin secretagogues • Impairment in renal function • Hyperkalemia • Genital mycotic infections • Hypersensitivity reactions • Increases in LDL-C 	<ul style="list-style-type: none"> • Volume depletion • Use with medications known to cause hypoglycemia
Pregnancy Category:	C <i>teratogenic effects in juvenile rats (renal)</i>	C <i>teratogenic effects in juvenile rats (renal)</i>	C <i>based on animal data from other SGLT2 inhibitors</i>

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/s/

AMARILYS VEGA
11/12/2013

CLAUDIA B MANZO
11/12/2013
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