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RESEARCH**

APPLICATION NUMBER:

204353Orig1s000

**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**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: July 11, 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 for the need of a REMS

Drug Name(s): Canagliflozin/metformin hydrochloride immediate release
fixed-dose combination

Therapeutic Class: Sodium glucose co-transporter 2 (SGLT2) inhibitor
(canagliflozin)/biguanide (metformin)

Dosage and Route: Oral tablets 50/500, 50/1000, 150/500, 150/1000 mg

Application Type/Number: NDA 204353

Submission Number: 0019

Applicant/sponsor: Janssen Pharmaceuticals, Inc.

OSE RCM #: 2014-376 and 2014-504

***** This document contains proprietary and confidential information ***
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 canagliflozin/metformin immediate release (IR) fixed-dose combination (FDC) (NDA 204353, proprietary name Invokamet[®]).¹ Janssen Pharmaceuticals is seeking approval for Invokamet as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets.

This NDA (204353) is a 505(b)(2) application; the listed drug is metformin hydrochloride (Glucophage[®]), tablet 1,000 mg for oral administration, Bristol-Myers Squibb Company, NDA 20357. Canagliflozin (NDA 204042) received FDA approval on March 29, 2013.

Janssen Pharmaceuticals did not submit a REMS or risk management plan with this application.

Please refer to DRISK's original review of this application dated November 4, 2013.

1.1 REGULATORY HISTORY

This application was initially submitted to FDA on December 12, 2012. FDA issued a Complete Response (CR) letter on December 11, 2013 because of insufficient data to support the existence of a robust relationship between plasma canagliflozin concentration and hemoglobin A1c (HbA1c) reduction.²

On February 10, 2014, the sponsor resubmitted this application and addressed the deficiencies cited by the FDA in the December 11, 2013 CR letter. A summary of postmarketing adverse events from spontaneous reporting and postmarketing studies that was inadvertently omitted from the February 10, 2014 submission was received by the Agency on February 14, 2014.

2 REVIEW FINDINGS

Data included in the February 10, 2014 and February 14, 2014 submissions are consistent with observations from clinical trials and the safety profile of canagliflozin.

3 CONCLUSION AND RECOMMENDATIONS

The data included in this class 2 resubmission does not add new safety information about Invokamet. The safety profile of this combination product remains consistent with that identified in clinical trials and the labeled risks for each individual product. Based on the available information, and because the drug entities are available separately, a REMS is not required for Invokamet.

Please contact DRISK if you have any questions.

¹Approved by FDA on May 2, 2014.

² FDA Complete Response letter, dated December 11, 2013.

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/s/

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**Department of Health and Human Services
Public Health Service
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Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: November 4, 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): Canagliflozin/Metformin Hydrochloride immediate release
fixed-dose combination

Therapeutic Class: Antihyperglycemic agent
Dosage and Route: Oral tablets 50/500, 50/1000, 150/500, 150/1000 mg

Application Type/Number: NDA 204353

Submission Number: Orig-1 received December 12, 2012

Applicant/sponsor: Janssen Pharmaceuticals, Inc.

OSE RCM #: 2013-293 and 2013-295

*** This document contains proprietary and confidential information that should not be released to the public. ***

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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 canagliflozin/metformin immediate release fixed-dose combination (NDA 204353, proposed tradename Invokamet[®]).¹ Janssen Pharmaceuticals is seeking approval for canagliflozin/metformin combination use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not adequately controlled on a regimen containing canagliflozin or metformin, or in patients who are already treated with both canagliflozin and metformin dosed as separate tablets. Janssen Pharmaceuticals did not submit a REMS or risk management plan with this application.

This NDA (204353) is a 505(b)(2) application; the listed drug is metformin hydrochloride (Glucophage[®]), tablet 1,000 mg for oral administration, Bristol-Myers Squibb Company, NDA 20357. At the time this application was submitted, canagliflozin (NDA 204042) was still under FDA review. Canagliflozin was subsequently approved by FDA on March 29, 2013.

1.1 BACKGROUND

Metformin Hydrochloride.^{2,3} Metformin hydrochloride (Glucophage[®] NDA 020357 and multiple other ANDAs) is an antihyperglycemic agent (biguanide class) initially approved on March 3, 1995 as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus. Metformin is the first-line drug of choice for the treatment of type 2 diabetes mellitus (T2DM), in patients without renal impairment. The extended release formulation, Glucophage XR, is not approved for use in children. Metformin improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It is contraindicated in patients with renal disease or renal dysfunction, known hypersensitivity to metformin, and acute or chronic metabolic acidosis (including diabetic ketoacidosis). The most serious safety concern identified with metformin is the risk for lactic acidosis; the product label contains a box warning for this risk. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function, thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. Alcohol intake potentiates the effect of metformin on lactate metabolism and should not be consumed in excess while a patient is being treated with metformin. In addition, metformin may decrease serum levels of vitamin B₁₂. A REMS was not required for Glucophage; all the risks associated with the use of metformin are currently managed through labeling only.

Canagliflozin.^{2,4} Canagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor approved by FDA on March 29, 2013 (tradename Invokana[®]) as an adjunct to diet and

¹ FDA communication to Applicant regarding proposed proprietary name, dated July 26, 2013: proposed proprietary name Invokamet was granted by the Division of Medication Error Prevention and Analysis in the Office of Surveillance and Epidemiology.

² Clinical Overview, Janssen, dated November 21, 2012.

³ Glucophage[®] (metformin hydrochloride) product label.

⁴ Invokana[®] (canagliflozin) professional product label.

exercise to improve glycemic control in adults with T2DM. Sodium-glucose co-transporters (SGLTs) have an important role in renal glucose reabsorption. SGLT2 in the proximal tubule of the kidney is responsible for the majority of glucose reabsorption. Inhibition of SGLT2 by canagliflozin results in a significant decrease in renal glucose reabsorption and consequently, in an increase in urinary glucose excretion, osmotic diuresis, and lower plasma glucose levels. Canagliflozin is contraindicated in patients with a history of a serious hypersensitivity reaction to canagliflozin and in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease or patients on dialysis. Important safety concerns identified for canagliflozin listed in the Warnings and Precautions section of the label include the following:

- hypotension (due to intravascular volume contraction)
- impairment in renal function (increases serum creatinine and decreases eGFR)
- hyperkalemia
- hypoglycemia (with concomitant use with insulin and insulin secretagogues)
- genital mycotic infections
- hypersensitivity reactions
- increases in Low-Density Lipoprotein (LDL-C)

A REMS was not required for canagliflozin; all the risks associated with the use of canagliflozin are currently managed through labeling.

*Canagliflozin/Metformin Fixed-dose Combination.*² Canagliflozin and metformin have complementary mechanisms of action, thus, it is expected that the combination of these agents should provide additive effects on improving glycemic control. The availability of a fixed-dose combination tablet consisting of canagliflozin and metformin provides an alternative to patients who are already on metformin and canagliflozin therapy dosed as separate tablets and to patients with inadequate glycemic control on a regimen containing only canagliflozin or metformin. In addition, the fixed-dose combination tablet is expected to improve convenience and compliance with antihyperglycemic therapy. The recommended starting dose of the canagliflozin/metformin combination is 50 mg canagliflozin with 500 mg metformin (or the current dose of metformin) twice daily with meals. Dose escalation should be gradual to reduce gastrointestinal side effects (associated to the metformin component). Renal function must be assessed prior to initiation of therapy and patients with creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females should not be started on the canagliflozin/metformin drug combination. The Applicant proposed four dose strengths, including 50/500 mg, 150/500 mg, 50/1,000 mg, and 150/1,000 mg, for twice-daily (bid) administration, with meals.

1.2 REGULATORY HISTORY

Following is the regulatory history of canagliflozin/metformin combination tablets, in pertinent part:

- **December 12, 2012:** NDA submission
- **January 24, 2013:** Filing meeting
- **March 29, 2013:** FDA approves canagliflozin.
- **May 14, 2013:** Mid-cycle meeting; identified clinical/statistical and clinical pharmacology deficiencies identified in the review process, in particular those related

to the bridging of studies using twice a day dosing of canagliflozin and studies using once a day dosing to support

- **May 29, 2013:** Post mid-cycle teleconference with the Applicant
- **June 5, 2013:** Post mid-cycle communication with Applicant.
- **September 26, 2013:** FDA sent to Applicant Late-Cycle Meeting Minutes.

Important upcoming dates:

- November 07, 2013: Wrap-up meeting
- December 12, 2013: PDUFA date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Clinical Overview, Janssen, dated November 21, 2012
- Canagliflozin Risk Management Review, Amarilys Vega, M.D., M.P.H, Division of Risk Management (DRISK), dated February 5, 2013
- FDA communication to Applicant regarding proposed proprietary name, dated July 26, 2013
- Metformin product label, 2013
- Invokana product label, 2013
- Invokamet proposed product label, draft dated August 15, 2013
- Wei Liu, Ph.D., Statistical Review, Division of Biometrics II, dated September 5, 2013
- Hyon J. Kwon, PharmD, MPH Clinical Review, dated October 31, 2013

3 RESULTS OF REVIEW

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

3.1 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM^{5,6}

The development program for the canagliflozin/metformin combination tablet references information from the canagliflozin single-agent NDA 204042 and from the Glucophage[®] NDA (20357). There have been no clinical efficacy studies conducted with the canagliflozin/metformin combination tablet; however, studies in healthy subjects demonstrated bioequivalence of canagliflozin/metformin combination tablet to canagliflozin and metformin co-administered as individual tablets. The Phase 3 clinical studies that provided the primary support for the canagliflozin tablet (NDA 204042) also provided the primary support for the canagliflozin/metformin combination with additional clinical data from a new Phase 2 study (DIA2003) and Phase 1 bioequivalence, relative bioavailability,

⁵ Clinical Overview, dated November 12, 2012.

⁶ Invokamet proposed product label, draft dated August 15, 2013.

food effect, and pharmacokinetic/pharmacodynamic studies.⁷ Please refer to DRISK REMS review of canagliflozin NDA 204042 for additional details regarding efficacy and safety findings.⁸

Canagliflozin is approved for once a day dosing while metformin requires dosing twice a day. The Applicant claims comparable pharmacokinetics and pharmacodynamics of the bid and the once-daily administration of canagliflozin and bridged a study using canagliflozin twice daily (Study DIA2003) with another study which used canagliflozin daily (QD) (Study DIA3006) to demonstrate that twice daily (BID) dosing will have similar efficacy in achieving glycemic control as daily dosing. However, the magnitude of HbA1c reduction in Study DIA2003 (dosing twice a day) was smaller than that observed in Study DIA3006 (dosing once daily). The Applicant attributed these findings to baseline differences in HbA1c between the two studies and conducted a simulation study (Bootstrap algorithm) to assess the impact of baseline glycemic control on the primary efficacy analysis. FDA statistical review notes the limitations of a post-hoc analysis and the difficulty of interpreting cross-trial comparisons.⁹ FDA clinical pharmacologists' interim assessment reported at the Late-cycle meeting, indicated that the pharmacokinetic (PK) and pharmacodynamics (PD) model employed by the Applicant to bridge the QD and BID dosing regimen was inadequate to support the exposure-response relationship for plasma canagliflozin and HbA1c response.¹⁰ At the time this review was completed, FDA and the Applicant were still discussing issues related to the PK/PD modeling.

3.2 SAFETY CONCERNS

The safety profile identified for the canagliflozin/metformin combination is consistent with the safety profile of each individual drug (see background section 1.1).¹¹ The risks listed in the Warning and Precautions section of the proposed label for Invokamet include the following:¹²

- lactic acidosis (box warning)

⁷ Clinical Overview, dated November 12, 2012, page 14: Bridge studies, "... 1) Phase 1 studies showing the bioequivalence of the CANA/MET IR FDC [*immediate release, fixed-dose combination*] combination tablet to the individual components (DIA1046, DIA1050, DIA1051, and DIA1038), along with a food effect study showing lack of food effect with the FDC tablet (DIA1037); 2) a Phase 1 study showing comparable pharmacokinetics and pharmacodynamics of bid and once-daily administered canagliflozin (at the same total daily doses of 100 mg and 300 mg) (DIA1032); 3) a Phase 2 18-week study in subjects with T2DM (DIA2003) showing comparable efficacy and safety/tolerability with bid administered canagliflozin (at total daily doses of 100 mg and 300 mg) in add-on use to metformin, as had been previously observed in the Phase 3 studies evaluating canagliflozin as add-on therapy to metformin; and 4) a pooled safety analysis of 26-week placebo-controlled Phase 3 studies of the add-on use of canagliflozin in subjects on metformin (alone or with another AHA [*antihyperglycemic agent*])."

⁸ Canagliflozin (NDA 204042) Risk Evaluation and Mitigation Strategy (REMS) Review, Amarilys Vega, M.D., M.P.H., Division of Risk Management (DRISK), dated February 5, 2013 – contains a summary of the Canagliflozin's drug development program including key efficacy and safety findings.

⁹ Wei Liu, Ph.D., Division of Biometrics II, Statistical Review, dated September 5, 2013.

¹⁰ Canagliflozin/metformin, Late-Cycle Meeting Minutes, dated September 26, 2013.

¹¹ Hyon J. Kwon, PharmD, MPH Clinical Review, dated October 31, 2013.

¹² Invokamet proposed product label, draft dated August 15, 2013.

- hypotension
- impairment in renal function
- hyperkalemia
- impaired hepatic function
- hypoglycemia
- genital mycotic infection
- hypersensitivity reactions
- vitamin B₁₂ deficiency
- increased LDL-C

4 CONCLUSION AND RECOMMENDATIONS

Available data to bridge canagliflozin QD and BID dosing regimen seems to be inadequate to support the exposure-response relationship for plasma canagliflozin and HbA1c response. FDA's assessment of the adequacy of PK/PD data is ongoing.

The safety findings are consistent with the labeled risks for each entity. Based on the available information, and because the drug entities are available separately, a REMS would not be an appropriate strategy to ensure the benefits outweigh the risks.

Please contact DRISK if you have any questions.

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