

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205649Orig1s000

**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 03, 2014

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

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Office of Medication Error Prevention and Risk
Management

Subject: Evaluation of the need for a REMS

Drug Name(s): Dapagliflozin/Metformin HCl Extended-Release,
Fixed Dose Combination

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

Dosage and Route: 5 mg dapagliflozin/500 mg metformin XR, 5 mg
dapagliflozin/1000 mg metformin XR, 10 mg
dapagliflozin/500 mg metformin XR, and 10 mg
dapagliflozin/1000 mg metformin XR - oral tablets

Application Type/Number: NDA 205649

Submission Number: Original (October 29, 2013)

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2013-2531 and 2013-2527

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

1 INTRODUCTION

This review documents DRISK's evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Dapagliflozin/Metformin extended-release (XR) fixed-dose combination (FDC) (NDA 205649). Bristol-Myers Squibb and AstraZeneca (BMS/AZ) are seeking approval for Dapagliflozin/Metformin XR FDC for the treatment of type 2 diabetes in adults as an adjunct to diet and exercise to improve glycemic control, administered once daily with [REDACTED]^{(b) (4)}. The proposed proprietary name, Xigduo XR, was approved November 24, 2013. BMS/AZ did not submit a REMS with this application but included an updated version of the global Risk Management Plan (RMP) for dapagliflozin.

1.1 BACKGROUND

Dapagliflozin (NDA 202293, Farxiga), a selective inhibitor of sodium glucose co-transporter 2 (SGLT2), was approved by FDA without a REMS on January 8, 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended starting dose of Farxiga is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Farxiga 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily. The warning and precautions section of the Farxiga label highlights the following safety concerns: hypotension, impairment of renal function, hypoglycemia, genital mycotic infections, increased LDL cholesterol, and bladder cancer. See DRISK reviews for dapagliflozin dated September 8, 2011 and November 23, 2011.

Metformin (NDA 020357, Glucophage), a biguanide initially approved by FDA on March 3, 1995, is approved as first-line treatment for use in adults with T2DM with normal or mildly impaired kidney function either as monotherapy or in combination with other oral antidiabetic drugs or insulin. Metformin XR (Glucophage XR) was initially approved by FDA on October 13, 2000. The metformin label has a boxed warning for lactic acidosis.

1.2 REGULATORY HISTORY

Following is Farxiga's regulatory history, in pertinent part:

- **October 13, 2013** – BMS/AZ submit a new application for Dapagliflozin/Metformin XR containing a Risk Management Plan (RMP).
- **November 24, 2013:** Proposed proprietary name, Xigduo XR, was approved.
- **January 8, 2014** – Farxiga (NDA 202293) received FDA approval. No REMS was required.
- **April 22, 2014:** Mid-cycle communication. No significant approvability issues identified. The Division of Metabolism and Endocrinology Products (DMEP) continued to support morning dosing due to concerns for the risk of adverse events associated with excessive urination at night, and an observation of an imbalance in adverse events for evening versus morning with dapagliflozin administration.
- **September 10, 2014:** Wrap-up meeting.
- **October 24, 2014:** PDUFA goal date.

2 MATERIALS REVIEWED

- Dapagliflozin/Metformin XR FDC, Clinical Overview, dated October 17, 2013.
- Dapagliflozin/Metformin XR FDC, Summary of Clinical Safety, dated October 15, 2013.
- DRISK reviews for Dapagliflozin: Amarilys Vega, MD, MPH, reviews dated September 8 and November 23, 2011.

3 CLINICAL DEVELOPMENT PROGRAM¹

The dapagliflozin clinical development program included 12 Phase 3 studies that support the safety and tolerability of dapagliflozin/metformin XR FDC tablets:

- One Phase 3 dapagliflozin monotherapy study (Study MB102013) supporting the safety and tolerability of once daily dosing with (b) (4).
- Eleven Phase 3 studies supporting the safety and tolerability of dapagliflozin in combination with metformin
 - Nine studies in patients with T2DM (Dapagliflozin + Metformin Pool)
 - Eight placebo-controlled studies (Dapagliflozin + Metformin Placebo-controlled Pool): Studies MB102014, MB102021, MB102034, D1690C00006, D1690C00010, D1690C00012, D1690C00018, and D1690C00019
 - 1 active-comparator study: Study D1690C00004
 - Two studies in patients with T2DM and hypertension: Studies MB102073 and MB102077

In addition, five biopharmaceutics studies contributed relative bioavailability (BA) or bioequivalence (BE) data for the dapagliflozin/metformin XR FDC.

Key Efficacy Findings: Use of dapagliflozin in combination with metformin was associated with reductions in:

- HbA1C (range: placebo subtracted adjusted mean change from baseline from -0.0% to -0.7%; p-value compared to placebo: < 0.0001)
- Fasting Plasma Glucose (range: placebo subtracted adjusted mean change from baseline from -3.6 mg/dL to -29.2 mg/dL; p-value compared to placebo: < 0.5 to < 0.0001)
- Body weight (range: placebo subtracted adjusted mean change from baseline from -1.0 kg to -4.7 kg; p-value compared to placebo: < 0.0001)

The above reductions were measured at Week 12 (MB102073 and MB102077), at Week 52 (D1690C00004) and at Week 24 (remaining studies).

Key Safety Findings: No new safety issues were identified with the use of dapagliflozin in combination with metformin XR beyond those already identified for each individual product. The submitted RMP for dapagliflozin does not list any new safety issue related to the use of dapagliflozin in combination with metformin.

¹Dapagliflozin/Metformin XR FDC, Clinical Overview, dated October 17, 2013.

4 CONCLUSION AND RECOMMENDATIONS

Dapagliflozin/metformin XR FDC clinical development program demonstrated this combination is effective in the management of T2DM. There are no new safety concerns identified with the use of this combination product beyond those already identified for each individual product.

DRISK does not recommend a REMS for managing the risks associated to dapagliflozin/metformin XR FDC.

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/s/

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07/03/2014

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