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RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

**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: December 20, 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

Drug Name(s): Dapagliflozin

Therapeutic Class: Antihyperglycemic, SGLT2 Inhibitor

Dosage and Route: 5 mg or 10 mg, oral tablet

Application Type/Number: NDA 202293

Submission Number: Original, July 11, 2013; Sequence Number 0095

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2013-1639 and 2013-1637

*** 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 (NDA 202293). The proposed proprietary name is Forxiga. Bristol-Myers Squibb and AstraZeneca (BMS/AZ) are seeking approval for dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Bristol-Myers Squibb and AstraZeneca did not submit a REMS or risk management plan (RMP) with this application.

At the time this review was completed, FDA's review of this application was still ongoing.

1.1 BACKGROUND

Dapagliflozin. Dapagliflozin is a potent, selective, and reversible inhibitor of the human renal sodium glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion.

Dapagliflozin's initial application, submitted December 28, 2010, demonstrated dapagliflozin's efficacy in improving glycemic control in adults (with normal or mildly impaired renal function) with T2DM; however, it received a Complete Response (CR) letter dated January 17, 2012 due to safety concerns regarding a potential association between dapagliflozin and the risks of bladder cancer and hepatotoxicity.¹ There was an imbalance in cases of breast cancer (dapagliflozin 10 vs. 3 comparator) that raised some concerns but not as serious as the signal detected for bladder cancer. In addition, the Division of Metabolism and Endocrinology Products (DMEP) determined that additional data was necessary to confirm neutral Hazard Ratio (HR) for cardiovascular events (CV). The CR letter did not include a request for a REMS.

Dapagliflozin was approved by the European Commission on November 14, 2012 for the treatment of T2DM and is also approved and marketed in Australia (Oct-2012), Mexico (Mar-2013), New Zealand (June-2013), Brazil (July-2013), and Argentina (Sep-2013).

On July 11, 2013, BMS/AZ resubmitted their application for dapagliflozin including a response to the CR letter. The recommended dose is 5 mg or 10 mg film-coated tablet taken once daily at any time of the day regardless of meals.

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

¹ Complete Response Letter, dated January 17, 2012.

- Hypersensitivity reactions
- Increased in LDL-cholesterol

Canagliflozin was approved without a REMS; product label includes a Medication Guide. Other SGLT2 inhibitors under clinical development include empagliflozin, ipragliflozin, togogliflozin and luseogliflozin.^{2,3}

See Appendix for a side-by-side comparison of canagliflozin and dapagliflozin.

1.2 REGULATORY HISTORY

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

- **December 28, 2010** – BMS submits a new application for dapagliflozin containing a proposed Risk Management Plan (RMP) based on the European Union (EU) format.
- **July 19, 2011** – Advisory Committee meeting for dapagliflozin. The committee voted against dapagliflozin approval due to concerns about its safety (No-9, Yes-6), in particular the potential risks of bladder and breast cancer and of hepatotoxicity. The panel recommended obtaining additional information regarding these risks.
- **January 17, 2012:** FDA issues a Complete Response Letter due to the potential risks of bladder cancer and hepatotoxicity.
- **July 11, 2013:** BMS/AZ resubmits dapagliflozin NDA 202293; this application did not include a REMS or an RMP.
- **December 12, 2013:** Advisory Committee meeting for dapagliflozin (see section 4 below).
- **January 11, 2014:** PDUFA goal date.

2 MATERIALS REVIEWED

- FDA Complete Response Letter, dated January 17, 2012
- Reviewers' Guide, dated July 2013
- Response to Complete Response Letter: New Drug Application (NDA) Resubmission, dated June 24, 2013
- December 12, 2013 Advisory Committee Meeting FDA and Applicant's briefing document and slides.
- DRISK reviews: Amarilys Vega, MD, MPH, reviews dated September 8 and November 23, 2011.

² Kurosaki E, Ogasawara H.: Ipragliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors in the treatment of type 2 diabetes: preclinical and clinical data. *Pharmacol Ther.* 2013 Jul; 139(1):51-9.

³ Empagliflozin, (b) (4) was submitted for FDA review on March 5, 2013. At the time of this review this application was still undergoing FDA evaluation.

3 RESULTS OF REVIEW

The efficacy of dapagliflozin as monotherapy or in combination with other anti-diabetic agents to improve glycemic control in adults (with normal or mildly impaired renal function) with T2DM was established during the first review cycle. (See DRISK's reviews from September 8 and November 23, 2011 for additional details about dapagliflozin's clinical development program.)

The second review cycle included data from 9 new Phase 2b and 3 clinical studies along with long term data from previously submitted studies for a total of 24 studies. These data provided a greater than 50% increase in patient-years exposure since the initial NDA. Also included in this safety update are some data from 2 additional studies: a pilot study in type 1 diabetes and a study of twice daily dosing.

To address the hypothesis that dapagliflozin may confer cardiovascular benefit, the Applicant initiated on April 2013 the '*Dapagliflozin Effect on Cardiovascular Events*' (DECLARE) outcomes study. DECLARE is a randomized prospective clinical outcomes study that will provide up to 6 years of exposure to dapagliflozin.

Regarding dapagliflozin's efficacy and safety based on the data included in the July 2013 resubmission, FDA's reviewers reached to the following conclusions:⁴

- Efficacy
 - HbA1c reductions are modest but consistent across trials and similar to other recently approved antidiabetic drugs – efficacy limited to patients with normal renal function or mild renal insufficiency.
 - Dapagliflozin produces modest reductions in weight and systolic blood pressure.
- Safety
 - Numeric imbalance in cases of bladder cancer not favoring dapagliflozin remains.
 - A potential case of drug-induced liver injury (DILI) appears to be due to autoimmune hepatitis, but an association with dapagliflozin remains plausible.
 - Marked liver laboratory abnormalities remain similar between treatment arms.
 - SGLT2 inhibitors are associated with increased LDL-C, genital infections, urinary tract infections, renal impairment, and volume depletion.
 - Unknown risk for fractures with long-term use in vulnerable patient populations.

⁴ Frank Pucino, Pharm.D, MPH, Clinical Reviewer, Division of Metabolism and Endocrinology Products, December 12, 2013 Advisory Committee meeting slide presentation.

4 ADVISORY COMMITTEE MEETING DECEMBER 12, 2013

Panel members' voted on the following two questions:

- In accordance with FDA's Guidance for Industry titled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes", has the Applicant provided sufficient evidence that dapagliflozin, relative to comparators, has an acceptable cardiovascular risk profile?

Yes - 10

NO - 4

- Based on the information included in the briefing materials and presentations today, do the benefits of dapagliflozin use outweigh identified risks and support marketing of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus?

Yes - 13

NO – 1

The Advisory Committee panel recommended that, in addition to the conduct and completion of DECLARE to assess the cardiovascular safety of dapagliflozin, the Applicant and FDA must develop a postmarketing assessment plan for the potential risks of bladder cancer and hepatotoxicity. Although the most recently submitted safety data assuaged concerns about breast cancer, a panel member recommended close monitoring of the incidence of breast cancer among dapagliflozin users because the relatively high incidence of breast cancer in the general population may blur a potential causal association with exposure to dapagliflozin.

5 CONCLUSION AND RECOMMENDATIONS

Dapagliflozin's clinical development program demonstrated this drug is effective in the management of T2DM. Key safety concerns that require additional assessment include the potential risks for bladder and breast cancer and drug-induced liver injury. If approved, FDA is likely to require additional data collection to evaluate these risks through Postmarketing Requirements (PMRs) and enhanced pharmacovigilance. Dapagliflozin's risks of hypoglycemia (mainly when used concomitantly with insulin and insulin secretagogues) and the risks for genitourinary infections and volume depletion are considered class effects; similar risks associated to canagliflozin have been effectively managed through labeling, including a Medication Guide. Therefore, DRISK and DMEP determined that a REMS is not required to manage the serious risks associated to dapagliflozin.

The FDA's review of this application is still ongoing. DRISK will reevaluate the need for risk management measures beyond labeling if additional safety information becomes available.

Appendix 1. A Side-by-Side Comparison of Dapagliflozin and Canagliflozin

	DAPAGLIFLOZIN	CANAGLIFLOZIN
General Information		
Trade Name:	Forxiga <i>(pending final approval)</i>	Invokana
Sponsor:	Bristol-Myers Squibb and AstraZeneca	Janssen Pharmaceuticals, Inc.
NDA:	202293	204042
Class:	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
FDA Approval Date:	Pending	March 29, 2013
Risk Management of Key Safety Issues		
Boxed Warning:	None	None
Warning & Precautions:	<ul style="list-style-type: none"> • Bladder cancer • Hypotension • Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues • Impairment in Renal Function • Genital Mycotic Infections • Hypersensitivity Reactions • Increases in LDL-C <p style="text-align: center;"><i>[label still under review]</i></p>	<ul style="list-style-type: none"> • Hyperkalemia • Hypotension • Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues • Impairment in Renal Function • Genital Mycotic Infections • Hypersensitivity Reactions • Increases in LDL-C
Pregnancy Category:	C <i>teratogenic effects in juvenile rats (renal)</i>	C <i>teratogenic effects in juvenile rats (renal)</i>

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/s/

AMARILYS VEGA
12/20/2013

CYNTHIA L LACIVITA
12/20/2013
discussed with and signing for Claudia Manzo
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**

ADDENDUM

Date: November 23, 2011

Reviewer(s): Amarilys Vega, MD, M.P.H.
Risk Management Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D.
Risk Management Analyst Team Leader, DRISK

Division Director: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Drug Name(s): Dapagliflozin

Therapeutic Class: Antidiabetic agent

Dosage and Route: 5 and 10 mg film coated tablets; oral administration

Application Type/Number: NDA 202-293

Applicant/sponsor: Bristol-Myers Squibb (and AstraZeneca)

OSE RCM #: 2011-82

1. INTRODUCTION

The purpose of this review by the Division of Risk Management (DRISK) is to amend the September 8, 2011 review evaluating the need for a Risk Evaluation and Mitigation Strategy (REMS) for dapagliflozin. In the September 8 review, DRISK indicated there was no compelling reason to justify the implementation of a REMS; however, deferred comments regarding risk mitigation of the potential risk of bladder and breast cancer, hepatotoxicity, effect of proteinuria on efficacy, bone fracture and cardiovascular safety pending receipt of the additional information requested from the sponsors.

On October 20, 2011, the sponsor submitted 24-week datasets from studies D1690C00018 and D1690C00019, triggering a major amendment to dapagliflozin New Drug Application (NDA). Additional data submitted by the sponsor included: (1) ad hoc analyses for D1690C00018 and D1690C00019 (submitted 11/8/11); (2) Study Reports for D1690C00018 and D1690C00019 (submitted 11/2/11); (3) updated Cardiovascular Meta-analysis; (4) and additional information regarding liver toxicity and cancer (submitted 10/27/11).

2. MATERIALS REVIEWED

DRISK reviewed the following documents:

- Clinical Review, Somya Dunn, Division of Division of Metabolism and Endocrinology Products, November 22, 2011.
- Statistical Review by Jonathan Norton, Division of Biometrics II, November 21, 2011.
- Statistical Review by Anita Abraham, Division of Biometrics III, November 22, 2011.
- Review of cases of liver injury in the clinical development program for dapagliflozin by Leonard Seeff, Division of Pharmacovigilance 1 (DPV1), November 21, 2011.
- Review of the Proposed Risk Management Plan for dapagliflozin, Amarilys Vega, Division of Risk Management, September 8, 2011.

3. RESULTS

The dapagliflozin review team reported updated safety finding on the following risks:

- Bladder cancer – updated findings support the initial assessment.
- Breast cancer – updated findings support the initial assessment. New cases of breast cancer identified in the control group suggest a more favorable safety profile for dapagliflozin.
- Hepatotoxicity – updated data findings are consistent with initial findings. No additional recommendations provided by DPV1 reviewers.
- Cardiovascular safety – updated data confirmed initial findings of the cardiovascular meta-analysis.

- Effect of proteinuria on efficacy – updated data suggests that protein binding is unlikely to influence dapagliflozin’s inhibition of renal glucose reabsorption.
- Bone fractures – no new data. Evaluation of this risk will be part of a large, randomized postmarketing cardiovascular outcomes study.

4. RECOMMENDATIONS

DRISK recommends managing identified safety risks through labeling and a Medication Guide. Additional risk management strategies such as a communication plan, and/or elements to assure safe use do not appear warranted at this time. Postmarketing safety studies include a large randomized cardiovascular outcomes study and ^{(b) (4)} observational pharmacoepidemiology studies. DRISK will provide additional comments and recommendations if the review division identifies new safety data warranting more extensive risk mitigation.

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/s/

AMARILYS VEGA
11/23/2011

CLAUDIA B KARWOSKI
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**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

INTERIM REVIEW

Date: September 8, 2011

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

From: Amarilys Vega, M.D., M.P.H.
Risk Management Analyst, DRISK

Cynthia LaCivita, Pharm.D.
Risk Management Analyst Team Leader, DRISK

Subject: Review of the Sponsors' Proposed Risk Management Plan
for dapagliflozin

Drug Name
(Established Name): Dapagliflozin

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

Dosage and Route: 5 and 10 mg film coated tablets; oral administration

Application Type/Number: NDA 202-293

Applicant: Bristol-Myers Squibb (and AstraZeneca)

OSE RCM #: 2011-82

TABLE OF CONTENT

1. INTRODUCTION.....	3
2. MATERIALS REVIEWED.....	3
3. BACKGROUND.....	3
3.1 Regulatory History.....	3
3.2 Dapagliflozin Clinical Development Program.....	5
4. SPONSORS' PROPOSED RISK MANAGEMENT PLAN.....	6
4.1 Identified risks.....	6
4.2 Potential risks.....	6
5. SAFETY CONCERNS IDENTIFIED BY FDA.....	7
5.1 Bladder cancer.....	7
5.2 Breast cancer.....	7
5.3 Hepatotoxicity.....	7
5.4 Urinary tract.....	7
5.5 Genital infections.....	7
5.6 Renal function.....	7
5.7 Bone Fracture.....	8
5.8 Cardiovascular.....	8
6. DISCUSSION AND RECOMMENDATIONS.....	8
7. APPENDIX.....	9

1. INTRODUCTION

The purpose of this review by the Division of Risk Management (DRISK) is to determine if a Risk Evaluation and Mitigation Strategy (REMS) is required for dapagliflozin.

Bristol-Myers Squibb (BMS) and AstraZeneca (AZ), referred to in this document as the sponsors, did not submit a REMS with the dapagliflozin application. However, included in the New Drug Application (NDA) submission was a Risk Management Plan (RMP) for dapagliflozin based on the European Union (EU) format.

Dapagliflozin is a first in class, potent, selective, and reversible inhibitor of the human renal sodium glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion.

Dapagliflozin is not authorized or launched in any country.

2. MATERIALS REVIEWED

DRISK reviewed the following documents:

- BMS & AZ, Dapagliflozin proposed Prescribing Information (PI) including a Medication Guide, submitted September 1, 2011.
- BMS & AZ, Dapagliflozin EU Risk Management Plan, dated August 10, 2011 and submitted August 26, 2011 (redline version submitted on September 7, 2011).
- Information Request Letter, sent by the FDA to BMS on August 15, 2011.
- Dapagliflozin Advisory Committee Meeting, FDA Slide Presentation, July 19, 2011.
- Dapagliflozin Advisory Committee Meeting, FDA Briefing Document, June 23, 2011.
- BMS & AZ, Dapagliflozin EU Risk Management Plan, dated November 29, 2010, submitted December 27, 2010.
- BMS & AZ, Dapagliflozin proposed Prescribing Information (PI), submitted December 27, 2010.

3. BACKGROUND

3.1 Regulatory History

- **December 27, 2010** – BMS submits a new application for dapagliflozin containing a proposed RMP based on the European Union (EU) format
- **July 19, 2011** – Advisory Committee meeting for dapagliflozin. The committee voted against dapagliflozin approval due to concerns about its safety (No-9, Yes-6), in particular the potential risks of bladder and breast

cancer and of hepatotoxicity. The panel recommended obtaining additional information regarding these risks.

- **August 15, 2011** – FDA sent an Information Request Letter to BMS requesting the following:
 - *Data from ongoing clinical trials*: six-month datasets for ongoing clinical trials D1690C000018 and D1690C000019.
 - *Liver safety information*: summary data on liver aminotransferases, bilirubin and other relevant tests, enzyme and/or bilirubin elevations exceeding 3X, 5X and 10X the upper limit of normal according to treatment group and dose; reports of all cases referred to the hepatic adjudication committee, and detailed information and case report forms for any potential Hy's Law cases; and the most current report from the Hepatic Adjudication Committee¹.
 - *Bladder cancer*: updated bladder cancer cases and incidence rate, including an analysis of risk factors at screening or baseline, and cases whose diagnosis was preceded by urinary or genital infections prompting increased urine monitoring.
 - *Breast cancer*: updated breast cancer cases and incidence rate, including analysis of risk factors at screening or baseline, and relevant medical/family history prior to baseline for the cases identified.
 - *Cardiovascular safety information*: updated cardiovascular meta-analysis to include major adverse cardiac events (MACE) reported in these two trials separately and combined with previously conducted meta-analysis.
 - *Information of efficacy in subjects with proteinuria*: all clinical data from the Phase 2b/ Phase 3 program correlating either categorical status of proteinuria (i.e., absent, micro or macroalbuminuria) or actual measures of urinary protein excretion (mg protein or albumin per gram of creatinine) at baseline and efficacy parameters (changes in HbA1c, changes in fasting plasma glucose, etc.).
- **August 26, 2011** – BMS submitted a revised version of the RMP, revised version of Annex 3 (list of ongoing studies of the RMP), a revised version of Annex 5 (draft protocols and draft synopses of the RMP), and a new Annex 9 (targeted questionnaires).
- **September 1, 2011** – BMS submitted a revised version of the label including a Medication Guide
- **September 7, 2011** – BMS submitted a redline version of the revised RMP.

A Type C meeting is scheduled for October 4, 2011 to continue the discussion of data from ongoing clinical trials; a revised pharmacovigilance plan including the potential

¹ Hepatic Adjudication Committee – the sponsors created this committee to adjudicate liver cases in Phase 3 clinical studies. Additional information in appendix 1, section 2.4.

risks of breast and bladder cancer; a medication guide to replace the proposed patient package insert; an update to the cardiovascular outcome trial synopsis; epidemiology protocols for liver failure, renal failure, bone fractures, and UTI complications; and an epidemiology study synopsis for cancer.

3.2 Dapagliflozin Clinical Development Program

Dapagliflozin sponsors, BMS and AZ, are pursuing approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The dapagliflozin clinical development program was conducted jointly by BMS and AZ. There were 26 pharmacology trials. The safety assessment was based on 3 Phase 2b, and 11 Phase 3 double-blind, placebo/active-controlled, randomized clinical studies; however, the main analyses of safety were performed on the short-term (ST) double-blind data in the Placebo-controlled Pool of Phase 2b and 3 studies (ST placebo-controlled pool) which included data after the initiation of rescue therapy. All of these studies were at least 12 weeks in duration and most were 24 weeks in duration. Most Phase 3 studies included a 1 to 4-week dietary/placebo lead-in period, with or without background anti-diabetic medication, followed by a 24-week, double-blind short-term treatment period. One Phase 3 study, D1690C00004 (direct comparison to sulfonylureas (SU), had a longer 52-week short-term double-blind treatment period. Eight of the Phase 3 studies included additional long-term treatment periods ranging from 24 to 156 weeks. There were 4,287 subjects with T2DM exposed to dapagliflozin and 1,941 subjects who had at least one dose exposure to control; this is 2.2 times more subjects exposed to dapagliflozin than to control.

Subjects with T2DM were treated with dapagliflozin as monotherapy; add-on combination therapy with a wide variety of other anti-diabetic medication; in direct comparison with sulfonylurea; as initial combination therapy with metformin; or in a dedicated study in subjects with moderate renal impairment.

The analysis of efficacy using HbA1c as endpoint showed dapagliflozin to be effective as monotherapy and in combination with other antidiabetic drugs.² Statistical analyses showed HbA1c decreased 0.5-0.6% following dapagliflozin treatment with the 10 mg once a day dose.³ Studies using Fasting Plasma Glucose (FPG) as the endpoint showed that dapagliflozin 5 mg and 10 mg doses were superior to the control at week 24 ($p < 0.001$). The estimated effect of the 10 mg dose ranged from a decrease in blood sugar from 17.5 to 25 mg/dL while the effect of the 5 mg dose ranged from 15.5 to 22.1 mg/dL. In addition, the combination of dapagliflozin and metformin demonstrated to be superior to each individual component ($p < 0.001$).

Proposed Indication

Dapagliflozin can be used as monotherapy or in combination (initial combination or add-on combination) with other antidiabetic agents. The recommended dose is 10 mg taken once daily at anytime of the day regardless of meals. However, for patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose may be appropriate.

² FDA presentation at the July 19, 2011 Advisory Committee Meeting, Silver Spring, Maryland.

³ The result of this analysis was based on the use of Last-observation-carried-forward (LOCF) as the primary imputation method.

4. SPONSORS' PROPOSED RISK MANAGEMENT PLAN

The RMP submitted by the sponsors on December 27, 2010 classified the risks into two main categories: identified risks and potential risks.

Following is a description of the risks identified by the sponsors and their recommended risk management activities.

4.1 Identified risks

Identified risks include increased risk of genital infections and increased risk of urinary tract infections (UTI). The sponsors believed that these risks could be adequately addressed in product labeling and through routine pharmacovigilance. The risk of UTI would be monitored in study D1690C000019, an ongoing study screening for asymptomatic bacteriuria. In addition, an epidemiology study is planned to estimate and compare the incidence of emergency room visit or hospitalization due to severe complications of UTI.

4.2 Potential risks

Potential risks include hypoglycemia, volume depletion, increased hematocrit, renal impairment/failure, bone fracture, and liver injury. The sponsors believe that these risks could be adequately addressed in product labeling and through routine pharmacovigilance. In addition, the sponsors have ongoing clinical trials and proposed additional studies to evaluate these risks further.

- Increased hematocrit - complete evaluation of data from study MB102035 and of sub-study of MB102035, which will measure erythropoetin and plasma volume.
- Renal Impairment/Failure - an epidemiology study is planned to evaluate the risk of hospitalizations for acute renal failure.
- Bone Fracture - study D1690C00012, a Phase 3 study to evaluate bone density by DXA as a safety objective with assessments at Years 1 and 2 and to study biochemical markers of bone formation and bone restoration, is scheduled for completion December 19, 2011. In addition, the sponsors are planning on another safety study including assessment of bone fractures.
- Liver injury - an epidemiology study is planned to evaluate the risk of hospitalizations for acute liver failure. The sponsors planned on a blinded adjudication of liver cases in Phase 3 clinical studies.

See Appendix 1 for a detailed description of the risk information included by the sponsors in the proposed Risk Management Plan.

On August 26, 2011, the sponsor submitted a revised RMP, which addressed the risks of breast and bladder cancer. However, the revised RMP did not include additional risk minimization measures.

5. SAFETY CONCERNS IDENTIFIED BY FDA

In reviewing dapagliflozin NDA clinical trials data, the FDA identified the following safety concerns as the most relevant to the analysis of benefit vs. risk:

5.1 Bladder cancer

There were 9 males with bladder cancer among subjects exposed to dapagliflozin versus 1 case (also a male) in the placebo group.

5.2 Breast cancer

There were 9 female subjects with breast cancer in the dapagliflozin-treated group and one case in the control group.

5.3 Hepatotoxicity

A potentially serious case of drug-induced liver injury (meeting the biochemical threshold for “Hy’s Law”) was reported in the development program.

5.4 Urinary tract

UTIs were more common among dapagliflozin treated patients (6.4% in the dapagliflozin treated group vs. 4.5% in the placebo group). Females had a higher percentage of infections than males. There was no dose response detected and there were no differences in the rate of pyelonephritis between dapagliflozin and the placebo groups. The long-term effect of increased UTI and genital infections on renal function and reproduction is unknown.

5.5 Genital infections

Genital infections occurred more frequently in the dapagliflozin-treated groups – 6.8% among all dapagliflozin treated subjects vs. 2.3% in the placebo group. The incidence of genital infections appeared to be dose-related. Females had higher rates of genital infection than males. In females, the adverse events were primarily vulvovaginal mycotic infections/vaginal infection and in males were balanitis and fungal genital infection. Most patients had only one episode of infection.

5.6 Renal function

The FDA is concerned about the short-term risks to renal function related to hypovolemia and dehydration in the elderly and in those patients on diuretic and antihypertensive therapy. Also of concern is the risk-benefit balance in patients with proteinuria.

Dapagliflozin mechanism of action results in increased glucosuria and increased diuresis. Renal-related adverse events in the placebo-controlled pool short and long-term treatment groups were balanced. However, there were 23 (1.1%) patients reported with blood creatinine increased in the dapagliflozin group vs. 4 (0.6%) placebo-treated patients in the short plus long term treated pool. Renal impairment and failure were reported in a higher proportion among dapagliflozin-treated patients with moderate renal impairment.

Adverse events involving volume depletion (hypotension, hypovolemia, dehydration) were reported more frequently in the dapagliflozin treatment groups (0.7% dapagliflozin groups vs. 0.4% in the comparator group during the short-term study period). The reactions were not dose-related and hypotension was the most common

adverse event. Because dapagliflozin is protein bound, its efficacy in patients with proteinuria could be decreased.

5.7 Bone Fracture

The dapagliflozin development program included monitoring markers of bone metabolism and the occurrence of fractures. The data reviewed did not suggest dapagliflozin has a clinically significant effect on bone loss or fracture. The fracture rate was low (1.4%) and balanced between dapagliflozin and control groups. However, FDA clinical reviewers recommend review of additional data the sponsors are currently collecting (study D1690C00012) and to continue monitoring for bone-related adverse events.

5.8 Cardiovascular

The sponsors conducted a cardiovascular safety meta-analysis including 14 phase 2b/3 trials. The pre-specified primary composite endpoint included the following adverse events: cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. There were 6,228 subjects in the database, 78 of which had a primary endpoint event (48 of 4,287 dapagliflozin subjects (1.1%) and 30 of 1,941 comparator subjects (1.5%)). For the primary endpoint, the hazard ratio of dapagliflozin vs. comparator (stratified by study) was 0.67 (98% CI: 0.38, 1.18) suggesting no increased risk of cardiovascular events with the use of dapagliflozin.

6. DISCUSSION AND RECOMMENDATIONS

Dapagliflozin clinical development program demonstrated its efficacy for decreasing HbA1c and fasting plasma glucose; however, based on safety concerns the FDA advisory panel voted against dapagliflozin's approval.

In addition to the risks identified by the sponsors, the FDA identified additional safety concerns including the potential risk of bladder and breast cancer, insufficient information about effect of proteinuria on efficacy, and the need for additional bone and cardiovascular safety information.

The imbalance in the cases of bladder and breast cancer in patients who received dapagliflozin is higher than what is reported in the literature. Reviewers from the Division of Epidemiology concluded that the clinical trials in the development program were not powered to distinguish a statistically significant difference between dapagliflozin and active treatment arms.⁴

The sponsors initially proposed to manage the known risks of dapagliflozin through labeling and to continue evaluating these risks through several postmarketing studies. To gain a better understanding of the risks associated with dapagliflozin, on August 15, 2011 the Division of Metabolism and Endocrinology Products (DMEP) requested that the sponsors submit additional safety and efficacy data.

A revised RMP submitted by BMS on 8/26/2011 included the risks of breast and bladder cancer but did not include additional risk minimization measures. In addition, the

⁴ Dapagliflozin Advisory Committee Meeting FDA Briefing Document, July 19, 2011.

sponsors submitted on September 1, 2011 a Medication Guide (MG) to replace the previously proposed patient package insert.

Based on the available data, the increased risk of urinary tract and genital infections, hypoglycemia, and hypovolemia and dehydration in the elderly and in those patients on diuretic and antihypertensive therapy could be adequately addressed in product labeling and in a MG.

DRISK will defer comments regarding risk mitigation of the potential risk of bladder and breast cancer, hepatotoxicity, effect of proteinuria on efficacy, bone fracture and cardiovascular safety pending receipt of the additional information requested from the sponsors.

At this time DRISK does not believe there is a compelling rationale for a REMS. Please notify DRISK if you have any questions.

7. APPENDIX

Appendix 1 – Summary of the Sponsors’ Proposed Risk Management Plan

1. Safety Concerns

The Risk Management Plan submitted by the sponsors on December 27, 2010 classified the risks into two main categories: (1) identified risks (genital infections and urinary tract infections) and (2) potential risks (hypoglycemia, volume depletion, clinical consequences of increased hematocrit, renal impairment/failure, bone fracture, and liver injury).

In addition, the sponsors acknowledged that there is missing or limited information regarding the following:

- **Pediatric population** – dapagliflozin was not studied in subjects <18 years.
- **Pregnancy** – there are no adequate and well-controlled studies of dapagliflozin in pregnant women. There were 3 pregnancies exposed to dapagliflozin in clinical trials resulting in 1 elective termination and 2 unknown outcomes. Pregnant rats exposed to dapagliflozin during the time period corresponding to second and third trimester of human pregnancy showed an increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.
- **Lactation** – it is unknown whether dapagliflozin and/or its metabolite are excreted in human milk. Studies in rats demonstrate that dapagliflozin is excreted in breast milk.
- **Elderly (> 75 years)** –dapagliflozin was not specifically studied in the elderly population.
- **Patients with severe renal impairment** – the focus of the clinical studies was on patients with moderate renal impairment given that the mechanism of action of dapagliflozin depends on the glomerular filtration rate (GFR).
- **Patients with moderate and severe hepatic impairment** – the safety and efficacy of dapagliflozin has not been specifically studied in this population.
- **Patients with congestive heart failure** (defined as New York Heart Association (NYHA) class III and IV) – a meta-analysis of cardiovascular events (i.e., CV death, stroke, myocardial infarction, and hospitalization for unstable angina) in the Phase 2b and 3 program showed that the primary events occurred at a rate of 1.11% in dapagliflozin-treated subjects and 1.64% in comparator-treated subjects, per patient-year and a hazard ratio of 0.67 (98% CI: 0.385, 1.178; 95% CI: 0.421, 1.078) when comparing dapagliflozin with comparator. However, information on patients with cardiac failure is limited given that patients with New York Heart Association (NYHA) classes III and IV heart failure (HF) were excluded from the Phase 2b/3 clinical program. Two ongoing Phase 3b studies (D1690C00018 and D1690C00019) are evaluating the safety and efficacy of dapagliflozin in subjects with T2DM, cardiovascular disease, and hypertension.

Identified Risks

1.1. Genital Infections

The proportion of subjects with genital infections was higher for dapagliflozin 167 (5.1%) vs. placebo 12 (0.9%) (ST placebo-controlled pool). Discontinuation due to genital infections was 0.2% in the dapagliflozin-treated group. Females had higher rates of genital infection than males. In females, the adverse events were primarily vulvovaginal mycotic infections/vaginal infection and in males were balanitis and fungal genital infection. Most patients had only one episode of infection.

1.2 Urinary Tract Infections

Events of UTI was higher for dapagliflozin 158 (4.8%) vs. placebo 52 (3.7%) (ST placebo-controlled pool). The percentage of discontinuation of therapy due to UTI was 0.3% in the dapagliflozin group. Most patients had only one episode of infection. The most frequent types of infection in both females and males were UTI and cystitis. Males also presented with balanitis and genital fungal infections. Only a small proportion of patients had pyelonephritis: dapagliflozin 2.5 mg (0.2%), dapagliflozin 5 mg (0.1%), dapagliflozin 10 mg (0%). This adverse event is potentially due to the glucosuria induced by dapagliflozin.

Potential Safety Concerns

1.3 Hypoglycemia

The proportion of dapagliflozin-treated subjects experiencing a major episode⁵ of hypoglycemia in the ST placebo-controlled pool was 0.02% vs. 0.1% in the placebo group. However, when used in combination with insulin or sulfonylureas, hypoglycemic events were more common overall and in the dapagliflozin groups than in the placebo group (7 (1.1%) dapagliflozin vs. 1 (0.5%) insulin; 1 (0.2%) dapagliflozin vs. 0 sulfonylureas). Only a few subjects discontinued study treatment due to hypoglycemia in both dapagliflozin and placebo.

1.4 Hypovolemia

The proportion of subjects with volume depletion-related events (hypotension, dehydration, or hypovolemia) was low in all treatment groups but slightly higher in the dapagliflozin group (24 (0.7%) dapagliflozin vs. 5 (0.4%) placebo). Overall, serious events occurred in \leq 0.2% of subjects and the events were balanced between dapagliflozin and comparator.

1.5 Clinical Consequences of increased hematocrit

Subjects in the dapagliflozin group had greater mean increases in hematocrit and hemoglobin in comparison to those in the placebo group. Mean changes from baseline to Week 24 in hematocrit in the ST placebo-controlled pool were 1.57%, 1.81%, and 2.15% in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and -0.40% in the placebo

⁵ Major episode of hypoglycemia: * Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration.

group. There was no clinical correlation established in the clinical development program. One subject had elevated hemoglobin (> 18 g/dL) or hematocrit (> 55.0%) with thrombotic adverse events (AE) in the dapagliflozin 5 mg group. However, this case was highly confounded by the presence of other risk factors.

1.6 Renal Impairment/Failure

Most reported events coded as PT “Increased creatinine”⁶ but there was no clinical correlation to this laboratory finding. In the ST placebo-controlled pool there were 38 (1.25%) subjects with events related to renal impairment or failure vs. 12 (0.9%) in the placebo group. There were 2 deaths related to renal impairment/failure: (1) 1 subject in the dapagliflozin 2.5 mg group in MB102013/MB10201312^{7,8} (during the long-term period) who had renal failure in the setting of worsening CHF subject treated with dapagliflozin 2.5 mg in study and (2) 1 subject in the placebo group in MB102029^{9,10} who had renal failure following myocardial infarction.

⁶ Based on coding utilizing the Medical Dictionary for Regulatory Activities (MedDRA) Preferred terms (PT)

⁷ MB102013 - Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of dapagliflozin as monotherapy in subjects with T2DM who have inadequate glycemic control with diet and exercise (US, Canada, Mexico, and Russia).

⁸ Subject (MB102013-94-530), a 69-year old white man treated with dapagliflozin 2.5 mg QPM, died on Day 367 due to acute renal failure presumed to be secondary to low volume or BP precipitated by worsening of cardiac failure (26 days after the study medication was discontinued). The subject had history of hypertension, dyslipidemia, and peripheral edema. On Day 242, the subject developed severe peripheral edema and was diagnosed with moderate cardiac failure. On Day 342, the subject was admitted to the hospital with severe cardiac failure. Study medication was discontinued due to the event with the last dose administered on Day 341. The cardiac failure improved on Day 345 and the subject was discharged from the hospital. He continued on treatment with furosemide and spironolactone. On Day 347, the subject was hospitalized due to fever, cough, and dyspnea and was diagnosed with severe pneumonia. The event was treated with clarithromycin and ciprofloxacin and resolved on Day 357 and he was discharged that same day. On Day 359, the subject was hospitalized with very severe acute renal failure (18 days after the study medication was discontinued) presumed to be secondary to low volume or BP precipitated by worsening of cardiac failure. His condition had not responded to medical treatment. On Day 367, the subject died due to acute renal failure that was considered by the investigator to be unrelated to study drug. (Case narrative obtained from page 224, Bristol-Myers Squibb & ASTRAZENECA AB, Dapagliflozin Clinical Safety Summary, November 29, 2010, submitted December 27, 2010).

⁹ MB102029 - Phase 2/3, a Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase 2/3 Trial to Evaluate the Glycemic Efficacy, Renal Safety, Pharmacokinetics, and Pharmacodynamics of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Moderate Renal Impairment Who Have Inadequate Glycemic Control (Argentina, Australia, Brazil, Canada, Denmark, France, India, Italy, Mexico, Peru, Puerto Rico, Singapore, Spain and US).

¹⁰ Subject MB102029-86-574, a 76-year-old male randomized to the placebo group with an approximate 12-year history of TD2M, received concomitant antidiabetic therapy with gliclazide and insulin. This subject's medical history included diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hypertension, coronary artery disease, and unstable angina. This subject died on Day 368 as a result of an acute MI (unadjudicated), complicated by cardiac failure (unadjudicated) and renal failure. In addition to the MI, the subject developed cardiac failure and renal failure at the same time. The last dose of study medication was given on Day 358. All 3 SAEs were considered by the investigator to be very severe in intensity and not related to study medication. (Case narrative obtained from page 224, Bristol-Myers Squibb & ASTRAZENECA AB, Dapagliflozin Clinical Safety Summary, November 29, 2010, submitted December 27, 2010)

1.7 Bone Fractures

In the ST placebo-controlled pool the proportion of subjects experiencing a fracture was lower in the dapagliflozin groups (14 (0.4%)) relative to the proportion in the placebo (10 (0.7%)). However, data from ST+LT, double-blind study (MB102029⁹) showed a higher proportion of fractures in subjects exposed to dapagliflozin (dapagliflozin 5 mg 3 (3.5%), dapagliflozin 10 mg 7 (8.2%)) vs. those exposed to placebo 0 (0%). Overall, no clinically important changes for mean serum concentrations of calcium, 25-hydroxyvitamin D (25[OH]VitD), and 1,25 dihydroxyvitamin D (1,25[OH]VitD) were observed. From baseline to Week 24, mean PTH levels decreased in the placebo group (0.6 pg/mL) and increased (1.8-2.6 pg/mL) in each dapagliflozin group. Although mean change from baseline in the markers of bone resorption was slightly higher in dapagliflozin- than placebo-treated subjects, changes in bone formation markers were inconsistent. A definitive conclusion on the effect of dapagliflozin on bone turnover in humans cannot be made at the time of submission.

1.8 Liver Injury

The proportion of subjects who experienced an increase in ALT and/or AST values above 3x the upper limits of normal (ULN) in the ST placebo-controlled pool was similar between dapagliflozin-treated group (33 (1.0%)) and the placebo group (17 (1.2%)).

A key finding was a report of drug induced hepatitis and probable autoimmune hepatitis in a 79 y/o Asian male¹¹ (subject D1690C00004-4402-6) treated with dapagliflozin in study D1690C00004¹². The subject had AT (AST and ALT > 20x ULN) and TBL (> 2x ULN) values while treated with dapagliflozin 5 mg. Dechallenge was positive. This case met the laboratory criteria for Hy's Law.

2 Risk Management Plans

The sponsors' Risk Management Plan addresses the identified and potential risks mentioned above through routine pharmacovigilance activities. To characterize the frequency, severity, causality, and nature of the risk for UTI, renal impairment/failure, clinical consequences of increased hematocrit, liver injury, and bone fracture, the sponsors will implement additional pharmacovigilance activities as listed below.

Routine pharmacovigilance activities include the following to address all the identified and potential risks:

- Targeted questionnaires for events of genital infections (serious), UTI (serious), renal impairment/failure and liver impairment.
- Supplemental CRFs to get more detailed information and assessment in clinical studies for genital infection, UTI, hypoglycemia and liver injury.

¹¹ Subject D1690C00004-4402-6 was subsequently identified as a 78 year old Indian male from the UK.

¹² D1690C00004 - Phase 3 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled study with a 52-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with combination with metformin in adult patients with T2DM who have inadequate glycemic control on metformin therapy alone. Enrolled 814 (406 receiving dapagliflozin), 52 week ST and 156 week LT. Estimated completion date Study Completion: 02-Jan-2013. (Argentina, France, Germany, Great Britain, Italy, Mexico, Netherlands, South Africa, Spain, Sweden)

- Evaluation/communication of potential risk in product labeling.
- Cumulative review of events of interest evaluated as requested by health authorities.
- Describe results of cumulative safety reviews in aggregate reports.
- Pharmacoepidemiology studies.

Additional pharmacovigilance activities targeting the risk for UTI, renal impairment/failure, clinical consequences of increased hematocrit, liver injury, and bone fracture:

2.1 Urinary Tract Infection

- **MB102103 ST** - Epidemiology program for characterization of emergency room visit or hospitalization due to severe complications of UTI (study protocol submitted to FDA see April 14, 2011 in Annex 5, Observational Study Protocol MB102103 ST, Comparison of the Risk of Severe Complications of Urinary Tract Infections Between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Anti-Diabetic Therapies
- **D1690C000019**: Phase 3 study, screening for asymptomatic bacteriuria. It is a 24-week, multicentre, randomized, double-blind, age-stratified, placebo controlled study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM and cardiovascular disease who exhibit inadequate glycemic control on usual care. Enrolled 553 (blinded, approximately 276 receiving dapagliflozin). Duration 24 week ST/28 week LT. Estimated completion date is November 24, 2011.

2.2 Renal impairment/failure

- **MB102104 ST**: Epidemiology program for characterization of hospitalization for acute renal failure. Observational Study Protocol MB102104 ST Comparison of the Risk of Acute Renal Failure and Acute Hepatic Failure between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Oral Antidiabetic Treatments.
- **MB102035**: Measured change in GFR over 12 weeks is being evaluated for dapagliflozin alone and in combination with hydrochlorothiazide. A sub-study of MB102035 will evaluate measured erythropoetin and plasma volume.

2.3 Clinical Consequences of Increased Hematocrit

- CV blinded adjudication in Phase 2b and 3 clinical studies.
- **MB102035¹³**: Measured change in GFR over 12 weeks is being evaluated for dapagliflozin alone and in combination with hydrochlorothiazide. A sub-study of MB102035 will evaluate measured erythropoetin and plasma volume.

¹³ MB102035 (Phase 2): Exploratory study to assess the effect of dapagliflozin on glomerular filtration rate (GFR) in subjects with T2DM who have inadequate glycemic and blood pressure (BP) control. Measured change in GFR over 12 weeks is being evaluated for dapagliflozin alone and in combination with hydrochlorothiazide (Completed 12/2/2010). A sub-study of MB102035 will evaluate measured erythropoetin and plasma volume.

2.4 Liver Injury

- **MB102104 ST:** Epidemiology program for characterization of hospitalization for acute renal failure. Observational Study Protocol MB102104 ST Comparison of the Risk of Acute Renal Failure and Acute Hepatic Failure between Patients with Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Oral Antidiabetic Treatments.
- Blinded adjudication of liver cases in Phase 3 clinical studies. Hepatic events and certain liver laboratory abnormalities will be adjudicated by an independent committee to determine the probability that drug-induced liver injury is the cause of liver-related events/abnormalities. Criteria for adjudication:
 - Confirmed AST and/or ALT > 3x ULN and TB > 1.5x ULN (within 14 days on or after the AST and/or ALT elevation).
 - AST and/or ALT > 5x ULN.
 - Liver-related serious or non-serious AE leading to discontinuation from study treatment.
 - Death associated with liver-related SAE.

2.5 Bone Fracture

- **D1690C00012** Phase 3 study to evaluate bone density by DXA as a safety objective with assessments at Years 1 and 2 and to study biochemical markers of bone formation and bone resorption. This is a 24-week, multi-centre, international, double-blind, randomized, parallel group, placebo-controlled study with a 78-week extension period to evaluate the effect of dapagliflozin in combination with metformin on body weight in T2DM subjects with inadequate glycemic control on metformin alone. Enrolled 182 (89 receiving dapagliflozin). Duration 24 week ST, 78 week LT. Estimated completion date is December 19, 2011.
- Safety study including assessment of bone fractures (details to be determined)

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/s/

AMARILYS VEGA
09/08/2011

CLAUDIA B KARWOSKI
09/08/2011
concur