

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier M.D.C.M
Subject	Division Director Summary Review
NDA/BLA #	202293
Supplement #	
Applicant Name	Bristol-Myers Squibb
Date of Submission	July 11 th 2013
PDUFA Goal Date	January 11 th 2014
Proprietary Name / Established (USAN) Name	Farxiga (Dapagliflozin)
Dosage Forms / Strength	Oral Tablets/5 and 10 mg
Proposed Indication(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Frank Pucino, Pharm D, MPH
Statistical Review	Wei Liu, PhD and Eugenio Andraca-Carrera, PhD
Pharmacology Toxicology Review	Mukesh Summan, PhD
CMC Review/OBP Review	Xavier Ysern, PhD
Clinical Pharmacology Review	Ritesh Jain PhD
OPDP	Kendra Jones
CDTL Review	Karen Mahoney, MD
OSE/DEPI	Christian Hampp, PhD

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

1. Introduction

On July 11th 2013, Bristol-Myers Squibb re-submitted the new 505(b)(1) drug application (NDA) for dapagliflozin (Farxiga) tablets. The applicant is seeking an indication for the use of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus. Dapagliflozin is a member of the sodium glucose co-transporter 2 inhibitor (SGLT2 inhibitor) class of glucose lowering agents and would be the second FDA-approved SGLT2 inhibitor indicated for the treatment of type 2 diabetes mellitus.

2. Background

Bristol-Myers Squibb submitted the NDA for dapagliflozin for the first time on December 28, 2010. The data in the initial submission did not support a conclusion that the benefits of dapagliflozin outweighed its risks and on January 17, 2012, a Complete Response Letter (CRL) was issued.

With regards to benefits, dapagliflozin was shown to have glucose lowering benefit in patients with normal renal function and in patients with mild renal impairment [estimated glomerular filtration rate (eGFR) above 60 mL/min/1.73 m²]. The magnitude of the observed dapagliflozin glucose lowering effect, in this segment of the diabetes population, was similar and no greater than that observed for other oral anti-diabetic therapies. Dapagliflozin did not improve glycemic control in patients with moderate or severe renal impairment. It was noted therefore that the benefits of this therapy would not extend to approximately 20% of the population with diabetes in the US¹ estimated to have moderate or severe renal impairment.

With regards to risks, signals of concerns identified in the original application included: a case adjudicated as representing “probable” (i.e., likelihood \geq 50%) dapagliflozin-induced liver injury; an imbalance in breast cancer cases not favoring dapagliflozin in women [incidence rate ratio [95% confidence interval (CI)] in original submission of 4.41 (0.57, 200.9)] and an imbalance in bladder cancer cases not favoring dapagliflozin in men [incidence rate ratio (95% CI) in original submission of 5.1 (0.70, 222.6)].

As expected from the drug’s direct pharmacodynamic effect (i.e., glycosuria), glucose lowering with dapagliflozin was associated with consistent albeit small reductions in weight (i.e., attributed to urinary caloric loss) and blood pressure (i.e., attributed to volume contraction from osmotic diuresis). The impact of observed weight and blood pressure changes on important clinical outcomes was not characterized in the program. Nevertheless, relative to some classes of anti-hyperglycemic (i.e., insulin, thiazolidinedione [TZD],

¹ USRDS 2013 Atlas of CKD

sulfonylurea) these changes were considered potential benefits of the drug in the overall benefit-risk assessment.

To better understand the impact of non-glycemic dapagliflozin effects on cardiovascular (CV)-risk, FDA considered the results of the pre-specified meta-analysis of CV-risk received in the original submission. In this analysis, the estimated hazard ratio (HR) for CV-risk was below unity for dapagliflozin [HR based MACE+: 0.67 (95% CI, 0.38-1.18) based on 78 primary events]. Such data were at least consistent with the theory that a drug like dapagliflozin could have a potential beneficial effect on macrovascular outcomes in an appropriately designed trial.

The FDA asked for an updated CV-risk analysis in the form of a major amendment received in October 2011 to corroborate the initial findings promising with additional data. The estimate of CV-risk in this second analysis was closer to unity compared to the estimate in the pre-specified CV-risk analysis [HR for "MACE+": 0.82 (0.58, 1.15) based on 145 events].

In the October 2011 amendment, CV-analyses results from a subgroup of two trials (i.e., 18 and 19) were scrutinized as they were viewed as particularly useful. First, participants in these two trials were recruited because they had documented CV disease at baseline. Second, these two trials were the largest trials and contributed more than 40% of the CV events in the updated meta-analysis. Third and in contrast to participants in the glycemic efficacy trials, participants in trials 18 and 19 were more representative of the population of patient with diabetes in the US in that they were older, had longer standing diabetes and had more frequent associated co-morbid diseases (i.e., dyslipidemia, renal dysfunction, hypertension, obesity) at baseline. In the pool of patients participating in Trials 18 and 19 the point estimate (95% CI) for the hazard ratios of "MACE+" and MACE were 1.07 (0.64, 1.77) and 1.27 (0.69, 2.31) respectively. The estimated hazard ratios were noted to be discordant with the trend in the overall CV-safety database.

Thus, with the data available in the first cycle of review the FDA could not conclude with any level of confidence that dapagliflozin offered significant benefit over existing therapy to justify approval in light of the uncertainty around the identified risks and a CR was issued. In a future resubmission, the applicant was asked to submit additional clinical trial data, to include 52-week data for trials 18 and 19, and update analyses related to bladder cancer, breast cancer, liver safety and CV-risk.

In July 2012, the applicant filed a Formal Dispute Resolution Request appealing the CR decision. In September 2012, the dispute appeal was denied by Dr. Kweder and the path forward described in the CRL upheld.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Clinical efficacy was reviewed in the first review cycle and the reader is referred to reviews by Drs. Dunn, Norton, Irony, Parks and Rosebraugh for details.

To support the indication of improved glycemic control, the glucose lowering effect of dapagliflozin was evaluated in 10 phase 3 clinical trials. These trials were multi-center, multi-national, randomized and were carried out in a double-blind fashion up to the primary efficacy assessment time point. The variable used in the primary efficacy assessment in each of these trials was the difference in the change in hemoglobin A1c (i.e., HbA1c) from baseline between dapagliflozin treated subjects and control treated subjects.

One trial in the resubmission, **D²_010**, had not been previously reviewed. This trial compared the glucose lowering effect of dapagliflozin 10 mg to placebo at 24 weeks in patients who were not adequately controlled on a maximally effective doses of either a dipeptidyl peptidase-4 inhibitor (DPP-4i) alone or a combination of a DPP-4 and metformin (i.e., add-on to background DPP-4i trial).

² D: applicant trial code prefix D1690C00

Nine trials were submitted in the original application (refer to Dr. Norton's first cycle efficacy review). Six were placebo controlled trials and all had a primary efficacy assessment at 24 weeks. Three were active controlled trials; two had an efficacy assessment at 24 weeks and one at 52 weeks. A brief description of these nine trials follows.

Placebo Controlled Glycemic Efficacy Trials

Monotherapy Trials in Drug Naïve Subjects

- **MB_013 - 24-week trial**
 - Compared dapagliflozin (2.5, 5 and 10 mg) to placebo
 - This trial had a single³ blind 78-week controlled extension
- **MB_032 - 24-week (low dose) trial**
 - Compared dapagliflozin (1, 2.5, and 5 mg) to placebo

Add-on to Metformin Trial in Subjects not Optimally Controlled on ≥ 1500 mg/day of Metformin

- **MB_014 - 24 week trial**
 - Compared dapagliflozin (2.5, 5 and 10 mg) to placebo
 - This trial had a single blind 78-week controlled extension

Add-on to Sulfonylurea Trial in Subjects not Optimally Controlled on ≥ 4 mg/day of Glimepiride

- **D⁴_005 - 24 week trial**
 - Compared dapagliflozin (2.5, 5 and 10 mg) to placebo
 - This trial had a single blind 24-week controlled extension

Add-on to Thiazolidinedione Trial in Subjects not Optimally Controlled on ≥ 30 mg/day of Pioglitazone

- **MB_030 - 24 week trial**
 - Compared dapagliflozin (5 and 10 mg) to placebo
 - This trial had a double blind 24-week controlled extension

Add-on to Insulin Trial in Subjects not Optimally Controlled on ≥ 30 IU/day of insulin +/- OADs

- **D_006 - 24 week trial**

³ Single blind: Site and subjects remained blinded to treatment assignment but applicant was no longer blinded.

⁴ D: applicant trial code prefix DC1960C0

- Compared dapagliflozin (2.5, 5 and 10 mg) to placebo
- This trial had a single blind 24-week controlled extension followed by another single blind 56-week extension

Active Controlled Glycemic Efficacy Trials

Add-on to Metformin Trial in Subjects not Optimally Controlled on ≥ 1500 mg/day of Metformin

- **D_004 - 52 week trial**
 - Compared dapagliflozin (titrated from 2.5 to 10 mg) to glipizide (titrated from 5 to 20 mg)
 - This trial had a single blind 52-week controlled extension followed by another single blind 52-week extension.

Dual Therapy (i.e., Factorial Studies) in Drug Naïve Subjects

- **M_021- 24 week trial**
 - Compared dapagliflozin (5 mg) + metformin XR (up to 2000 mg) to metformin XR alone (up to 2000 mg) and then to dapagliflozin alone (5 mg)
- **M_034- 24 week trial**
 - Compared dapagliflozin (10 mg) + metformin XR (up to 2000 mg) to metformin XR alone (up to 2000 mg) and then to dapagliflozin alone (10 mg)

Glycemic Efficacy Trial in Renal Impaired Patients

Only one additional trial, **M_029**, was designed as a glycemic efficacy trial. This trial aimed to compare the glucose lowering effect of dapagliflozin (5 and 10 mg) to placebo at 24 weeks in renal impaired patients (stable eGFR ranging from 30 to less than 60 mL/min/1.73 m²) treated with any background anti-diabetic agent except metformin.

Phase 3 Trials Evaluating Effects Other than HbA1c reduction

The applicant submitted other trials which were not considered necessary and/or pivotal for the glucose lowering indication.

One trial included in the original NDA submission, **M_012**, was primarily designed to assess the weight lowering effect of dapagliflozin 10 mg compared to placebo at 24-weeks when added to background metformin therapy.

Two trials included in the 2011 major amendment, **M_018** and **M_019**, were enriched for individuals with cardiovascular disease and were primarily designed to compare the effect of dapagliflozin 10 mg and “standard of care” to placebo and “standard of care” on HbA1c

reduction at 24 weeks and on the proportion of individuals meeting all criteria of a 3-item composite endpoint (i.e., an absolute drop of 0.5% or more from baseline in HbA1c, and a relative drop of 3% or more from baseline for total body weight, and an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure [SBP]). Data from these trials were to be used in the event that the pre-planned meta-analysis of Phase 3 glycemic trials would not be sufficient to satisfy the pre-marketing CV-risk requirements. Trials **D_018** and **D_019** had planned, single blind, 28 week safety extensions but were extended further after issuance of the CRL.

Finally, two trials included in this re-submission, **M_073** and **M_077**, were primarily designed to assess the blood pressure lowering effect of dapagliflozin 10 mg compared to placebo at 12 weeks in patients with hypertension in patients on antidiabetic therapy receiving an angiotensinogen converting enzyme inhibitor or an angiotensin receptor blocker.

The efficacy results for the above listed trials are discussed in Drs. Liu's and Pucino's reviews and will not be further discussed here.

Efficacy in Patients with Normal or Mildly Impaired Renal Function

Dapagliflozin was demonstrated to provide superior glucose lowering compared to placebo after 24 weeks in patients with normal or mildly impaired renal function when used as monotherapy (MB_13, MB_32) and when added to maximally effective background doses of: metformin (MB_014), glimepiride (D_005), pioglitazone (M030), and a DPP-4i (M_010). Dapagliflozin also provided superior glucose lowering compared to placebo when added to background insulin (D_006).

The estimated, placebo-adjusted, HbA1c reduction across trials and doses ranged from 0.40% to 0.84%. This effect size range is consistent with effect sizes observed for other recently approved glucose lowering, oral, agents. In trials evaluating both the 5 and 10 mg dose of dapagliflozin, a modest but consistent dose to HbA1c response relationship is seen suggesting the 10 mg dose provides some additional benefit in terms of glucose lowering over the 5 mg dose.

Table 1 below summarizes the applicant's finding for the placebo-controlled trials in the modified intent-to-treat (mITT) population using last-observation-carried-forward (LOCF) to impute missing data. Drs. Liu and Norton repeated these analyses and performed a number of additional sensitivity analyses to confirm the robustness of the primary efficacy findings. Dr. Liu also performed pooled analyses to explore the effect of dapagliflozin across subgroups defined by baseline demographic and disease characteristics. No significant treatment-by-subgroup interactions were identified. Finally, secondary analyses relying on glucose-related variables other than change from baseline in HbA1c (e.g., fasting and postprandial plasma glucose, proportion of individuals reaching glycemic target) were consistent with analyses based on this variable.

Table 1: Placebo Adjusted Change in HbA1c (%) from baseline to end-of-treatment (mITT population LOCF) for the 5 and 10 mg dapagliflozin doses

Study (Weeks)	Treatment Arm	n	Baseline Mean (SD)	LS Mean Change (SE)	LS mean difference (95% CI)	p-value
Monotherapy in drug naïve patients						
MB_13 (24)	Dapa 10 mg	70	8.01 (0.952)	-0.89 (0.1199)	-0.66 (-0.96,-0.36)	<0.0001
	Dapa 5 mg	64	7.83 (0.916)	-0.77 (0.1134)	-0.54 (-0.84,-0.24)	<0.0005
	Placebo	75	7.79 (0.831)	-0.23 (0.1044)		
MB_32 (24)	Dapa 10 mg	N/A	N/A	N/A	N/A	N/A
	Dapa 5 mg	68	7.92 (1.035)	-0.82 (0.1217)	-0.84 (-1.17,-0.50)	<0.0001
	Placebo	68	7.80 (1.117)	+0.02 (0.1200)		
Add-on to background metformin						
MB_014 (24)	Dapa 10 mg	135	7.92 (0.818)	-0.84 (0.0724)	-0.54 (-0.74,-0.34)	<0.0001
	Dapa 5 mg	137	8.17 (0.964)	-0.70 (0.0722)	-0.41 (-0.61,-0.21)	<0.0001
	Placebo	135	8.11 (0.959)	-0.30 (0.0718)		
Add-on to background sulfonylurea						
D_005 (24)	Dapa 10 mg	151	8.07 (0.792)	-0.82 (0.0610)	-0.68 (-0.86,-0.51)	<0.0001
	Dapa 5 mg	142	8.12 (0.781)	-0.63 (0.0627)	-0.49 (-0.67,-0.32)	<0.0001
	Placebo	145	8.15 (0.741)	-0.13 (0.0625)		
Add-on to background thiazolidinedione						
M_030 (24)	Dapa 10 mg	140	8.37 (0.963)	-0.97 (0.0828)	-0.55 (-0.78, -0.31)	<0.0001
	Dapa 5 mg	141	8.40 (1.026)	-0.82 (0.0828)	-0.40 (-0.63, -0.17)	<0.0001
	Placebo	139	8.34 (1.003)	-0.42 (0.0834)		
Add-on to background insulin						
D_006 (24)	Dapa 10 mg	194	8.58 (0.818)	-0.90 (0.0515)	-0.60 (-0.74,-0.45)	<0.0001
	Dapa 5 mg	211	8.61 (0.893)	-0.82 (0.0493)	-0.52 (-0.66,-0.38)	<0.0001
	Placebo	193	8.46 (0.764)	-0.30 (0.0521)		
Add-on to background DPP4i +/- metformin (not previously reviewed)						
MB_010 (24)	Dapa 10 mg	223	7.90 (0.806)	-0.45 (0.0509)	-0.48 (-0.62,-0.34)	<0.0001
	N/A	N/A	N/A	N/A	N/A	N/A
	Placebo	193	7.97 (0.779)	+0.04 (0.0509)		

Efficacy in Patients with Moderately Impaired Renal Function

Dapagliflozin was not observed to have a statistically or clinically important glucose lowering effect in patients with moderate renal impairment. The applicant's primary analysis, confirmed by Dr. Norton, is shown below.

Table 2: Placebo Adjusted Change in HbA1c (%) from baseline to end-of-treatment (mITT population LOCF) in Subjects with eGFR < 60 mL/min/1.73 m²

Study (Weeks)	Treatment Arm	n	Baseline Mean (SD)	LS Mean Change (SE)	LS mean difference (95% CI)	p-value
M_029 (24)	Dapa 10 mg	85	8.22 (0.973)	-0.44 (0.1708)	-0.11 (-0.40, 0.17)	0.435
	Dapa 5 mg	83	8.30 (1.040)	-0.41 (0.1701)	-0.08 (-0.37, 0.20)	0.561
	Placebo	84	8.53 (1.285)	-0.32 (0.1701)		

In most placebo-controlled trials, the applicant had pre-specified secondary analyses to explore the effect of dapagliflozin on non-glycemic endpoints. Use of dapagliflozin was associated with small placebo-adjusted reductions in both systolic blood pressure (i.e., 2-3 mmHg) and body weight (i.e., < 5% at one year). These changes were predicted from the drug's pharmacodynamics (e.g., glycosuria leading to net caloric loss and osmotic diuresis). At this time, it is unknown whether these small changes in blood pressure and weight will meaningfully impact morbidity and or mortality.

8. Safety

The safety findings for dapagliflozin were reviewed during the first review cycle and the reader is referred to reviews by Drs. Dunn, Irony, Hampp, Parks and Rosebraugh for details. Drs. Pucino, Senior and Andraca-Carrera have analyzed general, liver and CV safety respectively in the re-submission. Drs. Ning and Schechter have reviewed the bladder and breast cancer cases respectively. Dr. Mahoney in her CDTL memorandum has summarized the update to major safety issues in the re-submission. The reader is referred to their reviews for details. This summary will focus on CV-safety, liver toxicity, bladder cancer, and breast cancer risks.

In the original submission, the primary assessment of safety was based on fourteen pooled trials: three 12-weeks Phase 2b trials and eleven Phase 3 trials. In October 2011, an update to CV-risk, bladder and breast cancer risk based on 19 pooled trials was provided (i.e., Major Amendment). In the re-submission 21 pooled trials comprised the aggregated safety database. This database is referred to as the 30 month safety update (i.e., 30 MSU) in reviews. Note that five phase 2b/3 trials were not included in the aggregated safety dataset (e.g., including the two anti-hypertension trials). At each time-point additional data from either ongoing trials or safety extensions of parent trials, if available, also contributed to exposure.

The number and types of studies included in the safety pools across the key review time-points is tabulated immediately below.

	2011 Original Submission (14 trials)	2011 Major Amendment (19 trials)	2013 Re-submission (21 trials)
Phase 2b	MB102008 (monotherapy) MB102009 (add-on insulin) D1692C00005 (Japan monotherapy)	+ + + MB102035 (renal function trial) MB102045 (insulin sensitivity)	+ + + + +
Phase 3 Placebo- Controlled	MB102013 (monotherapy) MB102032 (monotherapy) MB102014 (add-on metformin) D1690C00005 (add-on sulfonylurea) MB102030 (add-on TZD) D1690C00006 (add-on insulin) D1690C00012 (weight reduction) MB102029 (renal impaired)	+ + + + + +extension data +extension data +extension data D1690C00010 (add-on DPP4i) D1690C00018 (high risk CV+HTN) D1690C00019 (high risk CV)	+ + + + + + + +extension data +extension data +extension data +extension data +extension data MB102054 (China mono) D1692C00006 (Japan mono)
Phase 3 Active- Controlled	MB102034 (combo versus metformin) MB102021 (combo versus metformin) D1690C00004 (versus sulfonylurea)	+ + +extension data	+ + +extension data
+; data from previous pool included			

Dr. Andraca-Carrera summarized subject exposure and duration of exposure for dapagliflozin and comparators across safety databases used in the cardiovascular safety analyses on slide 10 of his advisory committee presentation. This summary is reproduced below to provide a general sense of the incremental data received at each key time-point in the dapagliflozin review. Compared to the October 2011 Major Amendment the re-submission represents a 15% increase in exposure duration to dapagliflozin and a 24% increase in exposure duration to comparator.

	2011 Original Submission (14 trials)	2011 Major Amendment (19 trials)	2013 Re-submission (21 trials)
Subjects			
Dapagliflozin	4287	5498	5936
Comparators	1941	3184	3403
Patient-Years			
Dapagliflozin	4344	5738	6594
Comparators	1849	3095	3831

CV-Risk Analyses

The pre-marketing CV-risk assessment was based on a pre-specified meta-analysis which occurred after completion of the 14 phase 2b/3 glycemic efficacy trials. CV-events in the dapagliflozin program were prospectively defined and collected. Qualifying events were adjudicated by a panel blinded to treatment assignment. The primary objective of the pre-specified meta-analysis was to demonstrate that the CV hazard associated with dapagliflozin use was no greater than 80% that of comparator. The analysis was based on a time to first event of the four item composite endpoint MACE+ which includes: CV death, myocardial infarction, stroke and hospitalization for unstable angina. The results of the CV-risk analyses for the pre-specified meta-analysis and for analyses done with additional data available in October 2011 and in the re-submission are shown below. All analyses exclude an upper 95% confidence margin of 1.8 (i.e., an 80% excess risk).

	<i>Pre-specified Meta-analysis (14 trials)</i>	<i>2011 Major Amendment (19 trials)</i>	<i>2013 Re-submission (21 trials)</i>
Number of Events	78	145	178
MACE+	0.67 (0.38, 1.18)	0.82 (0.58, 1.15)	0.81 (0.59, 1.09)

In the CRL, the applicant was asked to provide updated analyses of CV-risk in the subgroup of trials (i.e., Trials 18 and 19) where presence of cardiovascular disease (CVD) at baseline was a required criterion for enrollment. The results of these analyses for the endpoints of MACE+ and MACE (CV-death, non-fatal MI and stroke) are shown below. In this high risk subgroup, use of dapagliflozin was not associated with unacceptably high risk of MACE+. Finally with accrual of additional data, the estimated HR based on the more specific MACE endpoint moved closer to unity.

	<i>Trials 18 and 19 2011 Major Amendment (19 trials)</i>	<i>Trials 18 and 19 2013 Re-submission (21 trials)</i>
Number of Events	60	87
MACE+	1.07 (0.64, 1.77)	0.98 (0.64, 1.49)
Number of Events	43	61
MACE	1.27 (0.69, 2.31)	1.11 (0.67, 1.83)

Dr. Andraca-Carrera repeated the primary analysis of CV-risk across subgroups defined by demographic and disease characteristics. Results of these exploratory analyses were, in general, consistent with overall findings.

Dr. Andraca-Carrera notes a small imbalance (8 versus 2 on dapagliflozin and comparators respectively) not favoring dapagliflozin in the occurrence of CV-events within the first 30-days of initiating randomized therapy. The applicant interprets this observation as a chance finding and at the Advisory Committee (AC) meeting followed a similar line of reasoning as

used in the canagliflozin application where an early event imbalance was also observed. Namely, that this analysis is post-hoc, that interpretability is severely limited due to the small number of events, that the findings are in line with expected month to month variability for between group hazard rates and that hazard rates between 0-30 days in the dapagliflozin group is no greater than rates observed at later time points. The applicant may be correct, however, since this is the second SGLT2 program where an early imbalance in CV events is observed and given the plausibility that these events could result from an acute effect related to drug initiation (i.e., volume contraction/hemoconcentration) it should be followed. In light of the poor reliability of these findings, I do not recommend labeling this theoretical risk at this time but do recommend following this potential signal in the dedicated CVOT trial.

Liver Toxicity:

In the original application, uncertainty around the hepatotoxic potential of dapagliflozin arose due to a single case adjudicated as “probable” drug-induced liver injury.

Analyses based on routine laboratory monitoring were not suggestive of hepatotoxicity. Indeed, the proportion of patients with marked liver test abnormalities was similar between dapagliflozin and comparator treated subjects in the original and the October 2011 safety pools. The proportion of subjects with marked liver test abnormalities is again similar between groups in the 2013 re-submission safety pool (Refer to Table 8.3 in Dr. Mahoney’s review).

A drug causality assessment for seven dapagliflozin exposed cases with marked liver injury (i.e., ALT 3 times the ULN) and bilirubin elevation (>2 times the ULN) was performed by the applicant and FDA. In all seven cases, an etiology other than drug-induced liver injury was found to most likely explain the cause of liver injury. Additional follow-up data for the one case classified as due to “probable” drug-induced liver injury in the original application led to re-classification of the case as auto-immune hepatitis. This case is described in details in Drs. Senior, Pucino and Mahoney’s reviews.

With additional exposure no new hepatotoxicity signal arose and the case initially attributed to drug-induced liver injury is no longer attributed to this etiology. The additional data provides reassurance that dapagliflozin is not associated with a particularly high hepatotoxic risk.

Breast and Bladder Cancer Risk

In the original submission, more subjects randomized to dapagliflozin were diagnosed with breast and bladder cancer. Although the imbalance was numerically small, these cancers were observed to occur 2 to 5 times more frequently on dapagliflozin than on comparators. This large relative increase in a randomized controlled setting was the cause for concern in the original application.

With regards to bladder cancer, post-hoc analyses did not reveal an imbalance in baseline risk factors or hematuria to explain the observed findings. Furthermore, available data did not suggest individuals randomized to dapagliflozin underwent more urological procedures as a result of increased reported urinary symptoms to support a role for detection bias in generating the imbalance. In the 2011 review cycle, Dr. Hampp had compared the incidence rate observed in the program to an expected incidence rate derived using data from the Surveillance, Epidemiology, and End Results (SEER) database by means of a standardized incidence ratio (SIR). Bladder cancer incidence in the program was approximately 3 times more frequent than was predicted from the SEER data [SIR (95% CI); 2.80 (95% CI, 1.36 – 5.13)].

In non-clinical studies dapagliflozin and its metabolites were neither mutagenic, clastogenic or carcinogenic and based on these data the FDA does not believe dapagliflozin or its major metabolites have a direct carcinogenic effect. In the re-submission the applicant submits nonclinical data to support a position that use of dapagliflozin does not have a tumor promoting effect in humans. Dr. Summan in his review summarizes these new findings and the limitations of these data with regards to truly informing the risk to humans in the clinical setting. In short, these additional nonclinical data do not allow the FDA to definitely conclude that changes induced by dapagliflozin use (e.g., changes in urinary composition or changes to the bladder microenvironment) have no growth-promoting effect on bladder cancer cells in humans.

Breast Cancer

The table below summarizes the number of breast cancer cases, the breast cancer incidence rates and the incidence rate ratios for breast cancer in females for each of the three key review time-points across the pools of Phase 2b/3 trials. The initial estimated rate ratio decreased by > 50% with addition of three cases and the wide confidence margin spanning protection to high risk shows that that the original estimate was non robust.

	2011 Original Submission*		2011 Major Amendment (19 trials)†		2013 Re-submission (21 trials)‡	
	Dapa	Control	Dapa	Control	Dapa	Control
Cases (n)	9	1	10	3	12	3
Incidence Rate per 10,000 patient-years	37.2	9.2	37.0	22.0	40.0	19.0
Incidence Rate Ratio	4.04 (95% CI, 0.56 – 177.1)		1.90 (95% CI, 0.52 – 8.93)		2.47 (95% CI, 0.64 – 14.10)	

*Dr. Dunn’s July 2011 FDA AC presentation

†Dr. Hampp’s November 29th 2011 Review

‡Dr. Pucino’s 2013 Clinical Review and applicant’s 30 months safety update report.

The applicant and Drs. Schechter and Pucino performed a causality assessment on the 12 identified breast cancer cases. Breast cancer risk factors readily identifiable from the case summaries included advanced age and obesity. Two of the twelve cases on dapagliflozin occurred within 30 days of drug initiation and this temporal relationship is not consistent with a drug related etiology. Ten of the 12 cases were diagnosed within one year after initiating therapy. This also represents an unusually short exposure to disease latency. The majority of tumors identified were characterized as non-aggressive tumors on the basis of estrogen receptor positivity. It is unknown whether an imbalance in breast cancer was present at baseline since mammography was not routinely performed. Finally, data limitations do not allow one to reliably assess the potential contribution of within trial detection bias (i.e., enhanced screening in one group versus another) on the observed imbalance. In light of the case characteristics, weakening of the association in additional data and owing to limitation of the data Dr. Schechter concludes that findings of breast cancer likely represent a spurious finding. She does not recommend labeling this imbalance but does recommend following this signal in the post-marketing setting.

Bladder Cancer

The table below summarizes the number of bladder cancer cases, bladder cancer incidence rates and rate ratios in males for each of the three key review time-points. The incidence rate for bladder cancer in males for both groups has decreased nominally with additional exposure. The IRR has remained relatively stable. One additional case of bladder cancer in a female randomized to dapagliflozin captured after the data cutoff date for the 2013 re-submission is not shown in the table.

	2011 Original Submission		2011 Major Amendment (19 trials)		2013 Re-submission (21 trials)	
	Dapa	Control	Dapa	Control	Dapa	Control
Cases (n)	9	1	9	1	9	1
Incidence Rate per 10,000 patient-years	29.9	5.9	28.4	5.4	24.6	4.3
Incidence Rate Ratio (95% CI)	5.08 (95% CI, 0.70 – 222.6)		5.38 (95% CI, 0.84 – 122.2)		5.43 (95% CI, 0.712-245.10)	

*Dr. Dunn’s July 2011 FDA AC presentation

†Dr. Hampf’s November 29th 2011 Review

‡Dr. Pucino’s 2013 Clinical Review and applicant’s 30 months safety update report page 74.

The applicant, Drs. Ning and Pucino performed a causality assessment on the identified bladder cancer cases. Risk factors readily identifiable from the case summaries included male sex, advanced age and significant smoking history in six of the nine cases. One case had had previous exposure to pioglitazone but no history of smoking. Four cases were identified within 6 months or less of dapagliflozin exposure with two of these cases being detected in the first three months of treatment. In two cases these tumors were incidentally discovered

in subjects undergoing procedures for other medical conditions, in six cases hematuria triggered the work-up and in some trace hematuria was present on a retrospective review of baseline assessment. The majority of identified tumors (n=6) were low grade, non-invasive, tumors (Ta stage).

The applicant espouses the position that the bladder cancer signal is a spurious finding using a weight of the evidence argument. In making this argument the applicant points to: the absence of a signal in nonclinical studies, the absence of an overall malignancy signal in the pool of phase 2b/3 clinical trials, the presence of risk factors other than drug exposure in the reviewed cases, the finding that observed tumors in cases exposed to dapagliflozin were low grade and distribution of the types of tumors were similar to those expected in the general population, the possibility that bladder tumors may have preceded exposure to dapagliflozin based on observation of baseline hematuria in some cases, and the short latency between exposure to cancer detection compared to the latency observed for products known to be bladder carcinogens (e.g., cyclophosphamide).

Although the applicant's arguments are valid, Dr. Ning is unwilling to dismiss the association between dapagliflozin exposure and bladder cancer as due to chance entirely for reasons similar to those invoked in the first cycle of review. Namely that the estimated relative risk has remained stable and although non robust, is relatively strong with an estimated risk ratio > than 5-fold above comparator. Furthermore, the signal arose from a large randomized and controlled dataset (~10,000 patients). In a randomized program of that size, it is difficult to invoke selection bias, measurement bias or other confounders to explain the identified association. As stated above, during the first review cycle, post-hoc analyses performed with available data were unable to establish that baseline differences in ascertained risk factors between groups existed (e.g., smoking/baseline hematuria) or that dapagliflozin treated subjects underwent more urological assessments/procedures as a result of increased frequency of urinary symptoms to exclude a cause and effect relationship.

Overall, the data concerning a potential bladder cancer risk associated with dapagliflozin use are non-robust and the reliability of the signal is low as evidenced by the large uncertainty around the estimate of risk which spans the possibilities of a protective effect up to a large risk increase. Causality assessments performed by the applicant and Agency do not allow one to definitely implicate or exonerate dapagliflozin of this risk. Given the lack of robustness of this risk, I agree with the majority opinion at the Advisory Committee meeting that this identified signal does not preclude approval but will need to be addressed in the post-marketing setting.

9. Advisory Committee Meeting

Refer to Dr. Mahoney's CDTL for a complete summary. On December 12th 2013 an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting was convened to

discuss cardiovascular risk, malignancy risk, and liver toxicity issues in the dapagliflozin program. At the meeting's end the advisors were asked to vote on the following questions:

1. 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?

Vote Results: Yes =10, No=4, Abstain=0

The members who voted yes were of the opinion that the applicant had satisfied the pre-marketing CV-risk evaluation requirements laid out in the above cited Guidance for Industry and voted yes with the knowledge that a definitive cardiovascular outcomes trial was in progress. For the advisors who voted no, the data in the pre-marketing assessment were not robust enough to definitively answer the question. These advisors pointed to uncertainty with regards to the divergent risk estimates in specific subgroups, to changes in lipid parameters, and to imbalance in early events in explaining their vote. These advisors were also of the opinion that residual uncertainties would be addressed by the ongoing cardiovascular outcomes trial.

2. 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?

Vote Results: Yes =13, No=1, Abstain=0

The members who voted yes were of the opinion that the demonstrated benefits of dapagliflozin outweighed the identified risks and that the level of concern for the residual potential risks did not rise to an extent that would warrant additional pre-marketing studies. Members with expertise in oncology were not ready to completely dismiss the bladder cancer finding as due to chance but acknowledged that the large residual uncertainty around the estimate limited interpretability of the signal. These experts were not concerned enough to ask for additional pre-marketing data related to bladder cancer but did advise FDA to feature this imbalance prominently in labeling and to follow this potential risk in the post-marketing setting.

3. Pediatrics

Dr. Mahoney's CDTL memorandum summarizes the relevant pediatric issues for this product. Deferred pediatric studies required by section 505B(a) of the FDCA which will be required postmarketing are:

2121-1 A randomized, multicenter, parallel, single-dose study to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin in children, 10 to 17 years of age with type 2 diabetes mellitus (T2DM) receiving one of the three dose levels of dapagliflozin over the range of 2.5 to 10 mg. At least 30% of randomized subjects in each dose group will be 10 - 15 years of age.

Final Protocol Submission: April 2012
Study Completion: August 2014
Final Report Submission: February 2015

2121-2 A 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of dapagliflozin for the treatment of pediatric subjects ages 10 to <18 years of age with type 2 diabetes mellitus (T2DM), as add-on to metformin or as monotherapy, followed by a 26-week double-blind, placebo- or active-controlled extension period (Week 26 to Week 52). At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10 to 14 years and 15 to <18 years) will be female. Secondary safety endpoints should include the effect of dapagliflozin on mineral and bone metabolism, and the effect of dapagliflozin on growth.

Final Protocol Submission: August 2015
Study Completion: February 2020
Final Report Submission: August 2020

4. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

5. Labeling

Dr. Mahoney's CDTL memorandum summarizes relevant labeling issues for this product. At this stage unresolved issues include.

Starting Dose:

The applicant favors a starting dose of 10 mg unless the patient is deemed by the prescribing physician to be "at risk for hypovolemia." In these patients the 5 mg dose would be the recommended starting dose. I find this recommendation to be vague and I doubt it will be effective in mitigating identified hypovolemic risks associated with dapagliflozin use in the general population of patients with diabetes. In the summary of clinical efficacy the applicant identifies the following patients as being at risk: "elderly patients, who lack access to fluids, have autonomic dysfunction or a history of hypotension, or individuals treated with loop diuretics." Dr. Pucino in his review shows that in the short-term placebo-controlled study

pool (i.e., a pool of relatively young and healthy patients with diabetes), subgroups of individuals who were > 65 years of age (regardless of access to fluids), or used loop diuretics or had moderately compromised renal function were approximately twice as likely to experience a dapagliflozin related hypovolemic event. In practice many individuals with diabetes are elderly, have neuropathy and use anti-hypertensive and diuretics for co-morbid diseases. It is for example estimated that 11 million of the 26 million individuals with diabetes in the US are 65 years old or older⁵.

The Division favors a starting dose of 5 mg for all patients with the option to titrate up for additional glycemic benefit. Glycemic benefit was established for the 5 mg dose. Dapagliflozin is both a diuretic and a glucose lowering agent and this particularity sets it apart from other anti-diabetic agents (with the exception of canagliflozin). In pharmacodynamics studies the 5 mg dose produced less glycosuria, diuresis and volume loss than the 10 mg dose. Modest dose dependent early (Week 1) changes in serum creatinine and eGFR attributed to volume loss were seen in the clinical trial program. Hypovolemic/hypotensive events are directly related to the drug's diuretic effect.

In a phase 2b study (MB102035) the 10 mg dose was compared to hydrochlorothiazide 25 mg. In this study, dapagliflozin 10 mg caused a greater decrease in measured GFR (using iohexol clearance) and measured plasma volume compared to placebo and hydrochlorothiazide 25 mg at Week 12. Dapagliflozin 10 mg use was also associated with a greater rise in N-terminal prohormone of brain natriuretic peptide (hypothesized to reflect a compensatory natriuresis as result of increased red cell mass) than either placebo or hydrochlorothiazide. Increases from baseline in plasma renin activity and aldosterone levels were observed in the dapagliflozin 10 mg and hydrochlorothiazide group. Although not definitive these results further suggest that dapagliflozin 10 mg impacts intravascular volume.

The starting dose for any diuretic is the lowest effective dose and a titration approach to dosing is a rational approach for a diuretic drug like dapagliflozin. Titration ensures patients are not placed at undue risk by allowing treating physicians to assess tolerability at the lower dose and adjust co-administered medications if needed before escalating to the dose with a maximum diuretic effect. This is doubly important for a drug being used for its glucose lowering effect and not for its diuretic properties per se.

Finally we do not believe requiring titration will adversely impact patient outcome, the 5 mg dose is an effective dose and use of titration is common for anti-diabetic products (metformin, sulfonylurea, GLP-1). Caregivers routinely assess HbA1c response after initiating a new therapy and are accustomed to escalating the dose if glycemic response is inadequate.

⁵ Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

The applicant states that in glycemic efficacy trials evaluating both the 5 and 10 mg dose, the absence of a dose to hypovolemic event relationship suggests the 10 mg is safe for the general diabetes population. In my opinion, these trials lacked sensitivity to detect differences as they were performed in relatively healthy individuals and were not enriched for patients at most risk for hypovolemic complications [e.g., elderly patients, patients with mild renal dysfunction⁶ or for the presence of specific co-administered medications (e.g., anti-hypertensive or diuretic medications)]. The small numbers of individuals with these characteristics in the short-term placebo-controlled datasets attest to this.

Bladder Cancer Imbalance:

The applicant had proposed including non-specific malignancy language in the (b) (4) label. The Division prefers that the identified signal be described in the Warnings and Precautions section of the label. The bladder cancer imbalance was the basis for requiring a post-marketing study and the Warning and Precautions section of the label is appropriate for describing potential serious risks. As discussed in Section 8, although the applicant makes a case against a cause and effect relationship between dapagliflozin exposure and bladder cancer, a causal relationship cannot be entirely excluded with the data in the application. Until the applicant provides data refuting this signal prescribers and patients should be adequately informed that an imbalance not favoring dapagliflozin was detected in the clinical program.

6. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

I agree with the opinion of the review team and recommend approval.

In patients with type 2 diabetes who have normal or moderately impaired renal function dapagliflozin 5 and 10 mg provides durable and clinically meaningful reductions in glycemia in the monotherapy setting and as add-on therapy to maximally effective doses of metformin, sulfonylurea, insulin, TZD, and sitagliptin. The magnitude of glucose lowering provided by dapagliflozin 5 and 10 mg was similar to that provided by maximally effective doses of metformin at 24 weeks. Dapagliflozin, as a member of the SGLT2 inhibitor class, offers potential benefits not offered by other classes of anti-diabetic agents. Relative to insulin and insulin secretagogues dapagliflozin is not associated with a high risk of hypoglycemia. In contrast to insulin, insulin secretagogues, and thiazolidinediones dapagliflozin does not cause weight gain and in some settings causes a modest amount of weight loss. In contrast to all currently approved anti-diabetic agents except canagliflozin, dapagliflozin use results in a small reduction in SBP.

⁶ The modified Diet in Renal Disease equation (MDRD) used to categorized function is recognized to underestimate renal function in patients with mild to normal renal dysfunction further diluting the sensitivity in this subgroup.

Risks causally related to dapagliflozin identified in the program include genital mycotic infections and adverse reactions related to volume contraction including renal impairment events. In the patient population studied, these risks were in general not clinically serious and mitigation through appropriate labeling and monitoring is a reasonable approach.

The pre-marketing cardiovascular risk analyses do not suggest dapagliflozin is associated with unacceptable CV-risk to preclude approval. The applicant has initiated a cardiovascular outcomes trial to satisfy the post-marketing CV-risk assessment requirements for anti-diabetic products.

Results from routine monitoring of liver enzymes and review of causality in cases with significant hepatic injury and liver function abnormalities do not suggest dapagliflozin is hepatotoxic.

The findings of a numerical imbalance in breast and bladder cancer events identified in the application have been discussed in Section 8. These signals are driven by few cases and the estimates of risk are unstable as evidenced by the significant lowering of the estimated breast cancer risk with addition of two cases to controls. A causal relationship between dapagliflozin use and breast cancer is unlikely in the context of the overall data. A causal relationship between dapagliflozin use and bladder cancer diagnosis cannot be entirely excluded with the data in the application for reasons highlighted in Section 8. These potential risks will be followed in the post-marketing setting.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No postmarketing Risk Evaluation and Mitigation Strategies will be required.

- Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing studies (PMR) will be required under FDCA 505(o)3.

2121-3 A study to evaluate dapagliflozin in an orthotopic rodent bladder tumor promotion model.

Final Protocol Submission: November 2014

Study Completion: November 2015

Final Report Submission: August 2016

2121-4 An assessment and analysis of all foreign and domestic spontaneous reports of serious hepatic abnormalities and pregnancy outcomes in patients treated with dapagliflozin. The enhanced pharmacovigilance study should continue for 5 years.

Final Protocol Submission: September 2014
Interim Report Submissions: March 2015
March 2016
March 2017
March 2018
March 2019
Study Completion: September 2019
Final Report Submission: March 2020

2121-5 A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.

Final Protocol Submission: submitted May 9, 2013
Trial Completion: June 2019
Final Report Submission: June 2020

2121-6 To assess the risk of bladder cancer associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.

Final Protocol Submission: January 2015
Trial Completion: June 2024
Final Report Submission: December 2024

At the time of this review the dates and final language for some of the postmarketing required studies are under discussion.

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/s/

JEAN-MARC P GUETTIER
01/08/2014