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APPLICATION NUMBER:

205649Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	4 August 2014
From	Karen Murry Mahoney, MD, FACE
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 205649
Applicant	Bristol-Myers Squibb
Date of Submission	29 October 2013
PDUFA Goal Date	29 October 2014
Proprietary Name / Established (USAN) names	Xigduo™ XR dapagliflozin + metformin hydrochloride extended release (XR), fixed-dose combination
Dosage forms / Strength	Oral tablet Dapagliflozin 5 mg + metformin XR 500 mg Dapagliflozin 5 mg + metformin XR 1000 mg Dapagliflozin 10 mg + metformin XR 500 mg Dapagliflozin 10 mg + metformin XR 1000 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate
Recommended:	Approval

1. Introduction

Xigduo XR®, hereafter referred to as Xigduo or DAPA+MET, is a fixed-dose combination (FDC) of dapagliflozin (a sodium glucose cotransporter 2 inhibitor) and metformin hydrochloride (a biguanide). Xigduo is proposed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

For more complete information on Xigduo, see the various discipline reviews in DARRTS; findings of these reviews are summarized briefly below. For more indepth information regarding the efficacy and safety of the dapagliflozin component, please refer to discipline reviews and decisional memoranda from 2011, 2012, 2013 and 2014 for Farxiga® (dapagliflozin, New Drug Application [NDA] 202293).

This cross-discipline team leader (CDTL) review focuses on data specific to the combination of dapagliflozin and metformin; and on any differences between the findings of the Xigduo review and those of the prior Farxiga review.

2. Background

Type 2 diabetes mellitus (DM2) is one of the most prevalent diseases in the United States, having been diagnosed in over 7% of the U.S. adult population, and DM2 is rising in incidence. The actual incidence far exceeds 7%, because screening studies have revealed that undiagnosed diabetes is even more common than diagnosed diabetes (Cowie et al 2009). The disease exerts an enormous negative impact on the lives of patients. In the United States, diabetes is the leading cause of blindness among adults ages 20-74 years, of end-stage kidney disease, and of nontraumatic limb amputation. The cost of diabetes is enormous; in 2007, estimated direct medical costs were $174 billion, with an additional $58 billion in indirect costs such as disability, work loss and premature mortality (National Institute of Diabetes and Digestive and Kidney Diseases, National Diabetes Information Clearinghouse, accessed 20 Dec 2013). These costs continue to increase.

At present, most published guidelines recommend metformin as the first drug to be used in the treatment of type 2 diabetes. However, many (perhaps most) patients with type 2 diabetes will require an additional agent in order to achieve adequate glycemic control, particularly if the patient begins with a higher hemoglobin A1c (HbA1c) (Inzucchi et al 2012). Therefore, there is a need for agents which can be taken in combination with metformin for the treatment of DM2. Each of the currently available classes of drugs for the treatment of DM2 has its own set of limitations. Two particularly desirable attributes of a drug for the treatment of DM2 are a low incidence of hypoglycemia, and body weight neutrality (or a favorable body weight effect). The SGLT2i class and metformin appear to have both attributes.

Dapagliflozin's inhibition of SGLT2 blocks the primary method by which the kidney reabsorbs glucose, and results in excretion of glucose in the urine. Metformin lowers hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Dapagliflozin is approved in several other countries, including those in the European Union, and in Argentina, Australia, Brazil, Mexico and New Zealand. Metformin is approved widely throughout the world. At the time of submission, Xigduo was not approved in any country.

3. Chemistry, Manufacturing and Controls

Overall, the Chemistry, Manufacturing and Controls (CMC) team recommends approval of this NDA, pending Biopharmaceutics and Compliance inspections, which are pending as of 26 Jul 2014.

Please see Dr. Leginus' review (DARRTS 4 Apr 2014) for this product. A brief summary of the primary findings of the CMC review follows.

3.1. Drug Substances

Xigduo XR contains two drug substances, dapagliflozin propanediol monohydrate and metformin hydrochloride.

The dapagliflozin drug substance is dapagliflozin propanediol monohydrate, a (b) (4) (b) (4) 1:1:1 (b) (4) of dapagliflozin, propanediol and water. The active component, dapagliflozin (hereafter referred to as DAPA), is an orally active selective inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin reduces renal glucose reabsorption, leading to urinary glucose excretion. This drug substance was previously reviewed (DARRTS 31 Oct 2013) by Dr. Xavier Ysern in the original application for Farxiga® (dapagliflozin).

Metformin hydrochloride (HCl) is a biguanide which lowers hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. (b) (4)

3.2. Drug Product

Xigduo XR is formulated as a film-coated (b) (4) tablet for oral administration, containing immediate release dapagliflozin and extended release metformin HCl (hereafter referred to as MET). The applicant has developed four tablet strengths: DAPA 5 mg + MET 500 mg; DAPA 5 MET 1000; DAPA 10 MET 500; and DAPA 10 MET 1000. (b) (4)

Excipients include microcrystalline cellulose, lactose anhydrous, crospovidone, silicon dioxide, magnesium stearate, carboxymethylcellulose sodium, and hypromellose 2208 and 2910. All are of compendial grade. The (b) (4) film coat is not compendial grade; however, all components are compendial.

3.3. Impurities

The impurity profile of the FDC is similar to that of the individual components; no new impurities are formed during the manufacturing process.

Per International Committee on Harmonization (ICH) Q6A, microbiology evaluation is not required. The solid dosage form has been shown not to support microbial viability or growth.

3.4. Release Specifications

The proposed release specifications include dapagliflozin and metformin HCl identity (high-pressure liquid chromatography [HPLC] and infrared spectroscopy), assay (HPLC), degradants (HPLC), content uniformity and dissolution; and appearance, (b) (4)

total microbial count, and testing for *Eschericia coli*. All noncompendial analytical methods have been validated.

3.5. Stability

Following recommendations in ICH QE1, "Evaluation of Stability Data", Dr. Leginus recommends a shelf-life of 24 months for each of the four strengths of the FDC, when stored at controlled room temperature (20-25° C).

4. Nonclinical Pharmacology/Toxicology

Overall, the Pharmacology/Toxicology team recommends approval.

Please see Dr. Mukesh Summan's review (DARRTS 11 Jun 2014). Please also see Dr. Summan's previous review for dapagliflozin (NDA 202293, DARRTS 9 Dec 2013). Studies supporting the pharmacology toxicology evaluation included a 7-day rat toxicokinetic study, and a pivotal 3-month rat study. In both studies, dapagliflozin was administered alone, or coadministered with metformin.

In the 7-day repeat-dose toxicokinetic rat study, metformin exposure was unaffected by dapagliflozin coadministration. Dapagliflozin exposure was decreased in male rats when dapagliflozin was coadministered with metformin (dapagliflozin exposure 70% of that seen in absence of metformin). This degree of reduction was characterized as slight by Dr. Summan.

Overall, findings in the 3-month rat study were consistent with findings in the pivotal nonclinical toxicology studies for dapagliflozin monotherapy. New adverse findings were not noted. Treatment with dapagliflozin alone or coadministered with metformin was associated with "minimal to slight" vacuolation of the zona glomerulosa of the adrenal gland. This was interpreted as a pharmacodynamic response, possibly due to increased aldosterone production as a consequence of increased urinary excretion of sodium. The no observed adverse effect level (NOAEL) was 52x the maximum recommended human dose, for the combination of dapagliflozin and metformin.

In previous reviews, dapagliflozin was not found to be a direct carcinogen. No new reproductive toxicology data were presented.

5. Clinical Pharmacology/Biopharmaceutics

5.1. Clinical Pharmacology

Overall, the Clinical Pharmacology team recommends approval.

Please see Dr. Sista's review (DARRTS 14 Jul 2014).

Two pivotal clinical pharmacology studies were done to address bioequivalence, food effect, and steady state pharmacokinetics (PK).

In Study MB102100, the dapagliflozin 5 mg + metformin 500 mg XR FDC was found to be bioequivalent to the individual components of dapagliflozin 5 mg and metformin XR 500 mg, administered together under fed conditions.

In Study MB102092, the dapagliflozin 10 mg + metformin 1000 mg XR FDC was found to be bioequivalent to the individual components of dapagliflozin 5 mg and metformin XR 500 mg x2, administered together under fed conditions.

Both Studies MB102100 and MB102092 incorporated a fasting arm to evaluate food effect. Food decreased the C_{max} of dapagliflozin; however, areas under the concentration curve (AUCs) were similar for fasting and fed treatments. In the dapagliflozin NDA, food-induced reductions of this magnitude did not affect the inhibition of renal glucose reabsorption within the dapagliflozin dose range of 5 to 10 mg. Metformin pharmacokinetics were unaffected by food.

The following tables summarize the bioequivalence data for dapagliflozin and metformin.

Table 5.1.1: Dapagliflozin Bioequivalence and Food Effect Comparisons, Dapagliflozin 10 mg vs Xigduo XR FDC 10/1000

Comparison	$AUC_{0-\infty}$ ng-h/mL GM Ratio (90% CI)	C_{max} ng/mL GM Ratio (90% CI)	AUC_{0-t} ng-h/mL GM Ratio (90% CI)
FDC 10/1000 (fed) vs Dapagliflozin 10 mg Monocomponent	0.971 (0.948, 0.995)	0.937 (0.868, 1.010)	0.972 (0.950, 0.995)
FDC 10/1000 (fed) vs FDC 10/1000 (fasted)	0.922 (0.902, 0.942)	0.656 (0.605, 0.711)	0.921 (0.900, 0.941)

Source: Dr. Sury's review, pg 29, extracted from Table 7
Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; FDC = fixed-dose combination; FDC 10/1000 = fixed-dose combination tablet of dapagliflozin 10 mg and metformin 1000 mg; GM = geometric mean; XR = extended release

Table 5.1.2: Metformin Bioequivalence and Food Effect Comparisons, Metformin XR 500 mg x 2 vs Xigduo XR FDC 10/1000

Comparison	$AUC_{0-\infty}$ ng-h/mL GM Ratio (90% CI)	C_{max} ng/mL GM Ratio (90% CI)	AUC_{0-t} ng-h/mL GM Ratio (90% CI)
FDC 10/1000 (fed) vs Metformin XR 500 mg x 2 Monocomponent	0.979 (0.927, 1.034)	1.001 (0.957, 1.047)	0.974 (0.921, 1.031)
FDC 10/1000 (fed) vs FDC 10/1000 (fasted)	1.026 (0.959, 1.099)	1.016 (0.926, 1.114)	1.054 (0.980, 1.134)

Source: Dr. Sury's review, pg 30, extracted from Table 9
Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; FDC = fixed-dose combination; FDC 10/1000 = fixed-dose combination tablet of dapagliflozin 10 mg and metformin 1000 mg; GM = geometric mean; XR = extended release

Comparisons of the 5/500 FDC versus monocomponents were similarly bioequivalent and had similar food effect findings.

Total and peak exposures of dapagliflozin and metformin were similar at steady state compared to single-dose.

General clinical pharmacology characteristics of the individual components are discussed in Dr. Sista's review (beg pg 21), and are briefly summarized as follows:

Dapagliflozin:

- Absolute oral bioavailability of 10 mg dose = 78%
- High-fat meal decreases C_{max} by 50% and prolongs T_{max} by 1 hour, but does not alter AUC compared to the fasted state
- Dose proportionality exhibited
- 91% protein-bound
- Mean plasma terminal half-life 12.9 hours following single oral 10 mg dose
- Extensively metabolized; primary metabolism by UGT1A9; primary metabolite dapagliflozin-3-O-glucuronide (inactive)
- Primary elimination renal
- Because the primary mechanism of action is dependent on the presence of renal function, the drug becomes ineffective with progressive decline in estimated glomerular filtration rate (eGFR)

Metformin:

- Absolute bioavailability of 500 mg dose 50-60%
- Food increases absorption by 50%, but no effect on C_{max} or T_{max}; high- and low-fat have same effect
- Lack of dose proportionality with increasing doses (less than dose-proportional), due to decreased absorption rather than alteration in elimination
- Negligible protein-binding
- Plasma elimination half-life 6.2 hours; blood elimination half-life 17.6 hours; erythrocyte mass may be a compartment of distribution
- Excreted unchanged in urine and does not undergo hepatic metabolism or biliary excretion. Tubular secretion appears to be major route of elimination

Drug-drug interaction and intrinsic factor studies were evaluated with the dapagliflozin NDA.

The clinical pharmacology team recommends no dose adjustment in patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73m^2). Xigduo XR should not be used in patients with an eGFR <60 mL/min/m^2. The applicant proposes an eGFR-based recommendation for dosing in renal impairment (consistent with the dapagliflozin full prescribing information [FPI]) rather than a serum creatinine-based recommendation (as in current metformin labels). The clinical pharmacology and clinical teams are in concurrence with this, as the population excluded by the dapagliflozin eGFR-based recommendations will generally exclude patients who would have been excluded under the metformin serum creatinine-based recommendations. The CDTL notes that the applicant has changed the wording of Section 2.2 of the FPI for Xigduo somewhat compared to that for Farxiga, i.e. the

statement that no dosage adjustment is needed for patients with mild renal impairment (b) (4)

(b) (4)

5.2. Biopharmaceutics

The Biopharmaceutics team recommends approval, pending required inspections.

Please see Dr. Chen's review (DARRTS 2 Jul 2014).

Dr. Chen found the applicant's proposed dissolution method and acceptance criteria acceptable.

An *in vitro* alcohol dose-dumping study did not demonstrate alcohol dose-dumping potential, and therefore no alcohol dose-dumping human PK study was needed.

The applicant sought a biowaiver for the two middle strengths (DAPA 10 MET 500 and DAPA 5 MET 1000) and provided supporting comparative dissolution profile data. Dr. Chen found these data acceptable, and granted the biowaiver.

6. Clinical Microbiology

Per ICH Q6A, microbiology evaluation is not required. The solid dosage form has been shown not to support microbial viability or growth.

7. Clinical/Statistical- Efficacy

Overall, the statistical and clinical reviewers recommend approval, pending required inspections.

Please see Dr. Liu's statistical review (DARRTS 20 Jun 2014) and Dr. Vasisht's clinical review (DARRTS 11 Jul 2014).

7.1. Studies Supporting the Superiority of the Dapagliflozin-Metformin Combination Over the Individual Components

No studies were conducted with the actual FDC tablet. The efficacy and safety were supported by studies of the coadministration of dapagliflozin and metformin. As discussed earlier in the Clinical Pharmacology section, bioequivalence was demonstrated between the Xigduo FDC tablet and coadministration of the individual components.

Two major studies supported the superiority of the fixed-dose combination (i.e. coadministration of dapagliflozin and metformin) over the individual components. Studies MB102034 and MB102021, conducted in drug-naïve patients with type 2 diabetes, compared the change from baseline in HbA1c at 24 weeks for the combination of DAPA and MET to the individual components. Study -34 utilized the 10 mg DAPA dose, and -21 used the 5 mg DAPA dose. In these two studies, a total of 1241 drug-naïve patients with baseline HbA1c ≥7.5% and ≤12% were randomized to one of three arms: DAPA + MET, DAPA alone, or MET alone. Metformin was uptitrated weekly in 500 mg increments; mean MET dose achieved was >1900 mg in all groups, and the median MET dose achieved was 2000 mg.

For the primary endpoint of change from baseline to 24 weeks in hemoglobin A1c, the combination of dapagliflozin + metformin was superior to either component alone, for both the 5 mg and 10 mg comparisons, as shown in Table 7.1.1 below.

Table 7.1.1: Change from Baseline to 24 Weeks in Hemoglobin A1c, Combination Dapagliflozin + Metformin vs Individual Components, Studies MB102034 and MB102021

Study	Comparisons	Treatment Group	Baseline Mean HbA1c, %	HbA1c Mean Change from Baseline, %	Difference in HbA1c Change Between Combo and DAPA, %, mean (95% CI), p value	Difference in HbA1c Change Between Combo and MET, %, mean (95% CI), p value
102034	**DAPA 10 mg + MET XR vs DAPA 10 mg and vs MET XR**	**DAPA 10 mg + MET XR**	9.1	-2.0		
		DAPA 10 mg	9.0	-1.5	-0.5 (-0.7, -0.3), p <0.0001	
		MET XR	9.0	-1.5		-0.5 (-0.8, -0.3), p <0.0001
102021	**DAPA 5 mg + MET XR vs DAPA 5 mg and vs MET XR**	**DAPA 5 mg + MET XR**	9.2	-2.1		
		DAPA 5 mg	9.1	-1.2	-0.9 (-1.1, -0.6), p <0.0001	
		MET XR	9.1	-1.4		-0.7 (-0.9, -0.5), p <0.0001

Source: Applicant's Table 5, pg 31, Clinical Overview, subm 29 Oct 2013
Abbreviations: combo = combination; DAPA = dapagliflozin; HbA1c = hemoglobin A1c; MET = metformin; XR = extended release

Superiority of the combination over components was also shown for changes from baseline in fasting plasma glucose and body weight, as shown in Tables 7.1.2 and 7.1.3 below.

Table 7.1.2: Change from Baseline to 24 Weeks in Fasting Plasma Glucose, Combination Dapagliflozin + Metformin vs Individual Components, Studies MB102034 and MB102021

Study	Comparisons	Treatment Group	Baseline Mean FPG, mg/dL	FPG Mean Change from Baseline, mg/dL	Difference in FPG Change Between Combo and DAPA, mg/dL, mean (95% CI), p value	Difference in FPG Change Between Combo and MET, mg/dL, mean (95% CI), p value
102034	**DAPA 10 mg + MET XR vs DAPA 10 mg and vs MET XR**	**DAPA 10 mg + MET XR**	189.6	-60.4		
		DAPA 10 mg	197.5	-46.4	-13.9 (-20.9, -7.0), p <0.0001	
		MET XR	189.9	-34.8		-25.5 (-32.6, -18.5), p <0.0001
102021	**DAPA 5 mg + MET XR vs DAPA 5 mg and vs MET XR**	**DAPA 5 mg + MET XR**	193.4	-61.0		
		DAPA 5 mg	190.8	-42.0	-19.1 (-26.7, -11.4), p <0.0001	
		MET XR	196.7	-33.6		-27.5 (-35.1, -19.8), p <0.0001

Source: Applicant's Table 5, pg 31, Clinical Overview, subm 29 Oct 2013
Abbreviations: combo = combination; DAPA = dapagliflozin; FPG = fasting plasma glucose; MET = metformin; XR = extended release

Table 7.1.3: Change from Baseline to 24 Weeks in Body Weight, Combination Dapagliflozin + Metformin vs Individual Components, Studies MB102034 and 102021

Study	Comparisons	Treatment Group	Baseline Wt, kg	Body Wt Mean Change from Baseline, %	Difference in Body Wt Change Between Combo and DAPA, mean (95% CI), p value	Difference in Body Wt Change Between Combo and MET, mean (95% CI), p value
102034	DAPA 10 mg + MET XR vs DAPA 10 mg and vs MET XR	DAPA 10 mg + MET XR	88.6	-3.3		
		DAPA 10 mg	88.5	-2.7	NR	
		MET XR	87.2	-1.4		-2.0 (-2.6, -1.3), p <0.0001
102021	DAPA 5 mg + MET XR vs DAPA 5 mg and vs MET XR	DAPA 5 mg + MET XR	84.2	-2.7		
		DAPA 5 mg	86.2	-2.6	NR	
		MET XR	85.8	-1.3		-1.4 (-2.0, -0.7), P <0.0001

Source: Applicant's Table 5, pg 31, Clinical Overview, subm 29 Oct 2013
Abbreviations: combo = combination; DAPA = dapagliflozin; MET = metformin; NR = not reported; wt = weight; XR = extended release

In the proposed labeling (FPI Table 11), the applicant includes the comparisons between DAPA 10 mg + MET and the individual components.

The CDTL notes that the applicant also proposes to include comparisons between DAPA monotherapy and MET monotherapy. For this comparison, DAPA 10 mg was noninferior to MET for HbA1c, but superior to MET for FPG ((b) (4) , and superior to MET for body weight reduction (mean difference -1.4 kg; 95% CI -2.0, -0.7; p <0.0001). The CDTL has concerns about including comparative data between the highest dose of DAPA, and a variable dose of MET. However, these same data were included in the approved DAPA label. The concern is somewhat mitigated by the observation that the dose of metformin was titrated to a mean of >1900 mg in both metformin-containing treatment arms, which is very near the maximal dose of metformin possible under the study design. (b) (4) ,

(b) (4)

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In the proposed labeling for Xigduo, the text and table for the above study using the 10 mg DAPA doses are very similar to those in the dapagliflozin monotherapy label. (b) (4)

Additionally, in the section for this study, the applicant has added the following sentence (which does not appear in the DAPA mono label):

(b) (4)

Similar sentences also have been added to multiple other sections in the proposed Xigduo FPI. The CDTL is concerned that this represents (b) (4) and requested removal of this and similar sentences throughout the FPI, and the applicant agreed to the removal.

The effect of Xigduo on systolic blood pressure is similar to that of DAPA (reduction by 3-4 mmHg).

7.2. Studies Supporting Other Efficacy Issues for which the Proposed Xigduo (Dapagliflozin-Metformin Combination) Prescribing Information Differs from the Farxiga (Dapagliflozin Alone) Prescribing Information

Aside from the issues discussed above, most of the language in the proposed Xigduo Full Prescribing Information is lifted verbatim from the Farxiga (dapagliflozin) prescribing information, and comes from studies in which dapagliflozin was coadministered with immediate-release metformin. All of these studies were reviewed by both the clinical and statistical review teams during the dapagliflozin review.

Discussed below is one efficacy issue for which data about a single study are presented differently in the proposed Xigduo FPI and the approved Farxiga prescribing information.

(b) (4)

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(b) (4)

7.3 Overall Efficacy Conclusions

The combination of DAPA and MET is more effective than the individual components for reduction of HbA1c, fasting plasma glucose, and body weight. Changes in body weight are modest.

(b) (4) are not recommended for inclusion in the FPI, because (b) (4)

8. Safety

Dr. Vasisht's review of the safety of Xigduo did not reveal any new safety issues beyond those previously described for dapagliflozin monotherapy and metformin monotherapy.

The primary data used to evaluate the safety of Xigduo were from a prespecified pool of eight placebo-controlled studies of DAPA coadministered with MET (either XR or immediate-release). Please see Dr. Vasisht's review, pages 18-22 (Table 4) for a summary description of the design of these trials. The mean duration of exposure for these trials was 23 weeks. For this pool, a total of 983 patients received DAPA 10 mg, 410 received DAPA 5 mg, and 1185 received PBO. Total DAPA+MET exposure (i.e. patients exposed to the combination of DAPA and MET) was 605 patient-years (PY). (When one adds all exposure from all trials which included DAPA and MET (e.g. active-controlled trials and extension periods), total DAPA+MET exposure was 2331 PY.) Please see Dr. Vasisht's review, Table 14, page 43, for a summary of exposure data by trial pool.

The incidence of death was similar in the DAPA 10 mg + MET (7 deaths, 0.6%) and PBO + MET (6 deaths, 0.8%) groups. There were no deaths in the DAPA 5 mg + MET group. Causes of death are reviewed on pages 50-55 of Dr. Vasisht's review. No particular cause of death was more common among DAPA group deaths compared to PBO group deaths.

Nonfatal serious adverse events (SAEs) occurred at a slightly lower numerical rate among DAPA-treated patients than among PBO-treated patients (DAPA 10 mg 4.1%; DAPA 5 mg 3.4%; PBO 5.1%). There were not marked differences in the incidence of any particular serious adverse event for DAPA+MET vs PBO (see Dr. Vasisht's review, Tables 17 and 18, beginning pages 55 and 58). Dr. Vasisht discusses a small imbalance in SAEs of pneumonia (DAPA 10 mg = 4 events, DAPA 5 mg = 1 event, PBO = no events). Review of the events did

not suggest causality by DAPA, and the number of events was too small to reach any meaningful conclusion.

In the primary safety pool, discontinuations due to adverse events occurred among 4%, 2% and 3.3% of patients in the DAPA 10 mg + MET, DAPA 5 mg + MET, and PBO groups, respectively. In the 10 mg group, the most common adverse events leading to discontinuation were renal/urinary (renal impairment 7 patients; blood creatinine increased, 2 patients; creatinine clearance decreased, 2 patients; urinary tract infection 2 patients). As discussed below, the CDTL recommends addition of information about renal adverse events to the FPI subsection of Section 6 which discusses safety information for the DAPA+MET combination.

Adverse events which were of special interest in the previous dapagliflozin review included bladder cancer, breast cancer, adverse liver events, genital mycotic infections, urinary tract infections, volume-depletion-related adverse events, and renal adverse events.

No new cases of bladder cancer were reported for this application.

When considering all studies (placebo- and active-controlled; short-term and long-term periods), there were five cases of breast cancer reported with DAPA 10 mg and two cases reported with PBO. It appears that all of these cases were included in the original DAPA review. During the DAPA review, Dr. Genevieve Schechter, the consultant from the Division of Oncology Products, stated that the small imbalance in breast cancer cases seen in the DAPA program may be a spurious finding.

No new serious hepatic adverse events were reported with this application.

Imbalances, not favoring DAPA+MET, occurred in similar proportions to those seen for the DAPA NDA, for genital mycotic infections, urinary tract infections, volume-depletion-related adverse events, and renal adverse events. As discussed below, in the proposed Xigduo FPI, in a subsection of Section 6.1 which specifically discusses the safety findings for the DAPA+MET combination, the applicant makes mention of the imbalance in genital mycotic infections and urinary tract infections, but does not mention renal events or volume-depletion-related events. As discussed below, the CDTL recommends addition to the Xigduo FPI of information about the imbalance of the two latter events.

There were no cases of lactic acidosis, an event of special interest for metformin. Gastrointestinal adverse events, which are common with metformin, did not occur with significantly different frequency for DAPA+MET versus PBO.

Regarding overall adverse events, Dr. Vasisht has provided a detailed review beginning on page 89 of her review. Of most importance to the CDTL are the events which the applicant proposes to include in the prescribing information.

Compared to the Farxiga FPI, for the Xigduo FPI, the applicant has added a separate subsection at the beginning of Section 6; this section specifically discusses adverse event data when dapagliflozin is combined with metformin.

Data used to support this subsection were from the prespecified primary safety pool of eight placebo-controlled studies of DAPA coadministered with MET (either XR or immediate-release), described above.

In the proposed Xigduo FPI, the applicant includes (as the first table in Section 6) a table of adverse reactions which occurred in at least 2% of patients who were treated with either DAPA 5 mg + MET or DAPA 10 mg + MET, and which occurred more commonly in patients treated with DAPA than in patients treated with PBO + MET. These data are from the pool of eight PBO-controlled trials described above.

Table 8.1: Applicant's Proposed Table for Full Prescribing Information-
Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin (sic)

Adverse Reaction	% of Patients		
	Pool of 8 Placebo-Controlled Studies		
	Placebo and Metformin N=1185	Dapagliflozin 5 mg and Metformin N=410	Dapagliflozin 10 mg and Metformin N=983
Female genital mycotic infections*	1.5	9.4	9.3
Nasopharyngitis	5.9	6.3	5.2
Urinary tract infections†	3.6	6.1	5.5
Diarrhea	5.6	5.9	4.2
Headache	2.8	5.4	3.3
Male genital mycotic infections‡	0	4.3	3.6
Influenza	2.4	4.1	2.6
Nausea	2.0	3.9	2.6
Back pain	3.2	3.4	2.5
Dizziness	2.2	3.2	1.8
Cough	1.9	3.2	1.4
Constipation	1.6	2.9	1.9
Dyslipidemia	1.4	2.7	1.5
Pharyngitis	1.1	2.7	1.5
Increased urination§	1.4	2.4	2.6
Discomfort with urination	1.1	2.2	1.6

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial. (N for females: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg and metformin=430).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, pyelonephritis, urethritis, and prostatitis.

‡ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, balanoposthitis. (N for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).

§ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

These data are accurate, and do include all events which met the criteria for inclusion in the table. However, this set of events does not include other adverse events of interest, and these important events are also not discussed in the accompanying text. Two events for which there was an imbalance in the DAPA+MET studies, and for which the events are not mentioned in this section include volume depletion events, and renal impairment events.

The table below (Table 30 from page 80 of Dr. Vasisht's review) illustrates the small numerical imbalance in volume depletion events seen in the DAPA+MET studies.

Table 8.2: Volume Depletion Events, Dapagliflozin/Metformin Placebo-Controlled Pools

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	N = 1185	N = 410	N = 983
AE of volume depletion	5 (0.4)	4 (1.0)	12 (1.2)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	N = 776	N = 216	N = 772
AE of volume depletion	10 (1.3)	6 (2.8)	18 (2.3)

Source: Modified from ISS Table 26, Page 75
Abbreviations: AE = adverse event; DAPA = dapagliflozin; ISS = Integrated Summary of Safety; LT = long-term; MET = metformin; ST = short-term

Events of renal impairment or renal failure occurred slightly more commonly numerically among patients taking DAPA than among patients taking PBO, in the pool of eight studies used for the primary safety evaluation (called the ST pool in both Table 8.2 above and in Table 8.3 below). This small imbalance in renal events is illustrated below (Table 32 from page 81 of Dr. Vasisht's review).

Table 8.3: Adverse Events of Renal Impairment or Failure, Dapagliflozin/Metformin Placebo-Controlled Pools

Number (%) Patients with an Event	Placebo + MET n (%)	DAPA 5 mg + MET n (%)	DAPA 10 mg + MET n (%)
DAPA + MET Placebo-Controlled Pool (ST)			
N	1185	410	983
AE of renal impairment or failure	16 (1.4)	8 (2.0)	25 (2.5)
DAPA + MET Placebo-Controlled Pool (ST+LT)			
N	776	216	772
AE of renal impairment or failure	30 (3.9)	6 (2.8)	42 (5.4)

Source: Modified from ISS Table 29 (including data after rescue)

The CDTL recommends addition of information regarding the increased incidence of events from these two categories, to the FPI in Section 6, associated with the description of adverse events occurring in the DAPA+MET trials.

In general, the remainder of the safety information proposed for inclusion in the Xigduo FPI closely parallels that for the Farxiga and metformin FPIs. A few differences are noted, as discussed below.

In Section 5, "Warnings and Precautions", the headings which appear as "Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues" and "Impairment in Renal Function" in the Farxiga FPI have been replaced in the proposed Xigduo FPI by "Use with Medications Known to Cause Hypoglycemia" and "Use in Patients with Renal Impairment". In the CDTL's opinion, the Xigduo headings in these sections should be replaced with the headings used in the Farxiga FPI, as the Farxiga headings specify the adverse reactions under discussion, and the proposed Xigduo headings are more consistent with dosage instructions or limitations of use.

In Section 6, "Adverse Reactions", in the list of important adverse reactions which begins the section, (b) (4) is omitted and should be included.

For the remainder of the Xigduo Section 6, the applicant has maintained essentially all the data from Section 6 of the Farxiga FPI. This includes data from both combination therapy (DAPD + MET), and from DAPA monotherapy. One exception is that the table regarding hypoglycemia (Table 6 for Xigduo FPI; Table 5 for Farxiga FPI) includes only information for combination therapy with metformin in the Xigduo FPI. The numbers of events are the same for this population in both FPIs. The CDTL considers this acceptable.

Another issue to be considered is in regard to adverse event data evaluated for the question of whether Xigduo should be administered in the morning or in the evening. In the original proposed FPI for Xigduo XR, the applicant proposed dosing with (b) (4)

(b) (4) For Xigduo, the applicant provided data from Study MB102013, which actually evaluated both morning and evening dosing for both the 5 mg and 10 mg DAPA strengths, versus placebo. Please see Dr. Vasisht's review (pg 95, Table 37) for a summary of possible volume depletion-related adverse events which occurred in this study. There were few differences between morning and evening dosing; however, the overall number of events was small, limiting conclusions.

(b) (4) . Therefore, the Division requested that the applicant change the dosing instructions to specify morning dosing (b) (4), and in a teleconference on 7 Apr 2014, the applicant concurred.

Overall, the risk profile for Xigduo appears very similar to that for Farxiga.

9. Advisory Committee Meeting

No Advisory Committee meeting was held.

10. Pediatrics

The applicant proposes that its pediatric program for dapagliflozin be used to fulfill the Pediatric Research Equity Act requirements for Xigduo. In general, drugs for the treatment of type 2 diabetes have been granted a waiver for the study of children under 10 years of age, as type 2 diabetes is rare in this age group. This waiver was granted for DAPA, and is also appropriate for Xigduo. For DAPA, the applicant is conducting a pharmacokinetic/pharmacodynamic study in children ages 10-17 years, and a clinical study in the same group (Studies MB102091 and MB102138). The clinical study is designed to evaluate the efficacy, safety and tolerability of DAPA added on to MET. The CDTL and the clinical pharmacology review staff concur that these studies are adequate to fulfill PREA requirements for Xigduo.

The clinical, safety, and clinical pharmacology teams discussed whether there would be a need for a swallowing study of the Xigduo tablet. (b) (4) . Therefore, the size of the Xigduo XR tablet is not significantly larger than that of a metformin XR tablet. For this reason, the review team did not feel that a swallowing study was necessary. There was discussion with regards to this point at the Pediatric Review Committee held on September 3, 2014. The recommendation made at that meeting was to include a swallowing study due the large size of the tablet (see meeting minutes submitted to DARRTS by Jane Inglese on September 15, 2014).

11. Other Relevant Regulatory Issues

The applicant did not submit a Risk Evaluation and Mitigation Strategy (REMS) for this product. Drs. Vega and Auth of the Division of Risk Management concurred that a REMS is not necessary, because the FDC carries no new safety concerns beyond those identified for the individual components (review in DARRTS 5 Jul 2014).

As of 3 Aug 2014, Biopharmaceutics and Compliance inspections are pending.

12. Labeling

The proprietary name of Xigduo XR has been evaluated and found acceptable.

Please see Sections 7 and 8 for discussions of recommended edits to the Full Prescribing Information for Xigduo XR. The following is a brief summary of the recommended edits:

- Reinsertion (as appears in the Farxiga FPI) of the specific eGFR for the term "mild renal impairment" in the dosing instructions
- (b) (4)
- (b) (4) (as appears in the Farxiga FPI) (b) (4) in multiple areas throughout the Xigduo FPI.
- (b) (4)
- (b) (4)
- Restoration of the wording of heading titles regarding renal and hypoglycemic events in the Warnings and Precautions section to the wording used in the Farxiga FPI
- Restoration of (b) (4) (which appears in the Farxiga FPI) to the list of adverse events which appears at the beginning of Section 6 of the Xigduo FPI
- (b) (4)

13. Recommendations/Risk Benefit Assessment

The CDTL recommends approval of this application, provided the results of pending inspections are satisfactory. As of 4 Aug 2014, results of inspections by Compliance and Biopharmaceutics are pending.

Issues regarding the ratio of benefit to risk are discussed below.

Regarding benefit, Xigduo XR is effective in lowering hemoglobin A1c, to a greater degree than either dapagliflozin alone or metformin alone. Additionally, the individual components have several favorable attributes:

- Neither component increases weight, but rather each component, and the FDC, are actually associated with a small amount of weight loss. This is a very desirable attribute for a drug for the treatment of type 2 diabetes, which is strongly tied to obesity.
- Dapagliflozin is associated with a small decrease in systolic blood pressure (SBP). Control of cardiovascular risk factors, such as blood pressure, is very important in patients with DM2. Poor control of SBP increases cardiovascular and renal risk.
- Dapagliflozin alone, or with agents other than insulin or sulfonylurea, is not associated with hypoglycemia. Metformin also is not associated with hypoglycemia. Hypoglycemia is a major limiting factor in diabetes management.

Overall, these benefits outweigh the identified risks, the most significant of which are:

- A numerical, but not statistically significant, increased risk of diagnosis of bladder cancer, which was fully reviewed for the Farxiga application, and for which no new cases were reported in this application.
- Genital mycotic infections
- Urinary tract infections (nonserious)
- Volume-depletion-related events
- Nonserious renal impairment events

No Risk Evaluation and Mitigation Strategy is recommended.

No postmarketing requirements beyond those required for Farxiga are recommended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
10/28/2014
CDTL submitted on behalf of Dr. Karen Mahoney

JEAN-MARC P GUETTIER
10/29/2014
I concur.