CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205649
Supporting document/s:	0000
Applicant's letter date:	10.30.2013
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Product:	Dapagliflozin + Metformin XR (Xigduo™ XR)
Indication:	Type 2 Diabetes Mellitus (T2DM)
Applicant:	AstraZeneca
Review Division:	DMEP
Reviewer:	Mukesh Summan, PhD, DABT
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TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The proposed dapagliflozin plus metformin extended release (XR) fixed dose combination (FDC), film-coated tablet was submitted in accordance with 21 USC 505(b)1 for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise. Both drugs are approved for use as monotherapies for the same indication. BMS/AZ owns dapagliflozin and submitted a letter of authorization for DMF # (b) (4) and DMF # (b) (4), both for the metformin hydrochloride drug substance, owned by (b) (4).

Nonclinical studies were conducted using co-administration of dapagliflozin and metformin rather than the FDC and were reviewed under IND 106,890. This pharmacology/toxicology NDA review summarizes the pertinent previously reviewed studies.

Safety margins to expected human exposure were estimated for dapagliflozin using C_{max} = 136 ng/mL and AUC = 465 ng.h/mL plasma exposure at the proposed maximum recommended human dose (MRHD) of 10mg dapagliflozin. Safety margins to expected human exposure were estimated for metformin XR using C_{max} = 2251 ng/mL and AUC = 26,667 ng.h/mL at the MRHD of 2000mg metformin XR.

1.2 Brief Discussion of Nonclinical Findings

The sponsor is seeking the approval of dapagliflozin as a fixed dose combination (FDC) with metformin extended release (Xigduo™ XR). Dapagliflozin is a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), approved by the FDA January 8th 2014. Metformin extended release (XR) is a biguanide class insulin sensitizer antihyperglycemic agent approved by the FDA October 13th 2000.

The safety of the dapagliflozin and metformin XR fixed dose combination is supported by the 7-day rat toxicokinetic study and the pivotal three month rat study of the co-administered individual components.

In the 7 day toxicokinetic rat study dapagliflozin was administered alone or co-administered with metformin. Treatment with metformin alone or when co-administered with dapagliflozin does not alter metformin exposure. The co-administration of dapagliflozin with metformin has no effect on dapagliflozin exposure in female rats, but resulted in slightly reduced exposure of dapagliflozin in male rats.

In the three month rat study dapagliflozin was administered alone or co-administered with metformin. Treatment with dapagliflozin alone or co-administered with metformin resulted in minimal to slight vacuolation of the zona glomerulosa of the adrenal gland. This is considered to be a pharmacodynamic response due to likely increased aldosterone production as a consequence of increased urinary excretion of sodium.

Pharmacodynamic effects as a result of exposure to dapagliflozin alone or co-administered with metformin were also evident with glucosuria, polyuria and calciuria present. There were no toxicologically adverse or toxicokinetic drug-drug interactions following the co-administration of dapagliflozin with metformin in the rat. For the co-administered drugs in the rat, the NOAEL for dapagliflozin is 5 mg/kg (59x MRHD 10 mg dapagliflozin) without metformin and 5/150 mg/kg with metformin (52x MRHD 10 mg dapagliflozin and 1x MRHD 2000 mg metformin).

Overall, the co-administration of dapagliflozin with metformin was consistent with toxicological findings observed in pivotal nonclinical toxicology studies with the dapagliflozin monotherapy and did not yield new adverse findings. The nonclinical co-administration studies support the safety and approval of the fixed dose combination.

1.3 Recommendations

1.3.1 Approvability

AP (Approval)
Pharmacology/Toxicology recommends approval of NDA 205649.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The nonclinical sections of the proposed Xigduo™ XR label, have incorporated the information present in the labels for the approved individual products dapagliflozin and metformin XR (Glucophage XR), respectively.

Established Pharmacological Class (Highlights/Indications & Usage):
Xigduo™ XR is a combination of dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin XR, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)	Dapagliflozin: (b) (4) Metformin: (b) (4)
Generic Name	Dapagliflozin propanediol Metformin hydrochloride
Code Name	Dapagliflozin: BMS-512148 Metformin: BMS-207150-01

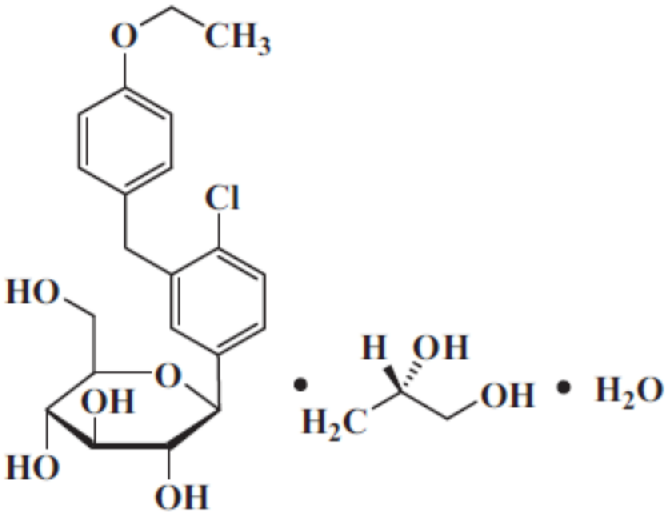
Chemical Name
Dapagliflozin: [redacted]

Metformin Extended Release (XR):
N,N-dimethylimidodicarbonimidic diamide [redacted] hydrochloride

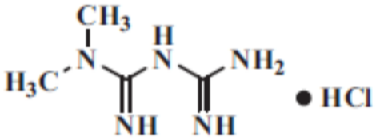
Molecular Formula/Molecular Weight
Dapagliflozin:
$C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$ / MW = 502.98 [redacted]

Metformin:
[redacted] / MW = 165.63 (monohydrochloride)

Structure or Biochemical Description: Dapagliflozin



Structure or Biochemical Description: Metformin



Pharmacologic Class
Dapagliflozin: Sodium Glucose co-Transporter 2 (SGLT2) Inhibitor
Metformin: Biguanide antihyperglycemic

2.2 Relevant INDs, NDAs, BLAs and DMFs

Dapagliflozin: IND 68,652 and NDA 202,293 (Farxiga®, AP January 8th 2014).

Metformin XR: NDA 21,202 (Glucophage® XR, AP October 13th 2000), from (b) (4) DMF's (b) (4) and (b) (4)

2.3 Drug Formulation

Dapagliflozin/Metformin XR (dapa/met XR) film coated tablets will be manufactured as dapa/met XR strengths as follows (mg/mg): 5/500, 10/500, 5/1000 and 10/1000.

Active ingredients: dapagliflozin and metformin extended release (XR)

Inactive ingredients: magnesium stearate, carboxymethylcellulose sodium, (b) (4) hypromellose 2208, hypromellose 2910, microcrystalline cellulose (b) (4), silicon dioxide, lactose anhydrous, crospovidone (see sponsor's table below) and a film coating layer: (b) (4) orange, pink and yellow, respectively (see sponsor's table below).

Table 1. Composition of Dapagliflozin/Metformin XR Tablets (sponsor's table)

Component	Quality Standard	Function	Quantity per Tablet (Dapa/Met XR mg/mg)			
			5/500	10/ 500	5/1000	10/ 1000
(b) (4)						
Metformin Hydrochloride/ (b) (4)	In-house[b]	Active				(b) (4)
Carboxymethylcellulose Sodium (b) (4)	USP	(b) (4)				
Hypromellose 2208	USP, Ph.Eur.					
Hypromellose 2910	USP					
Microcrystalline Cellulose (b) (4)	NF, Ph.Eur.					
Silicon Dioxide	NF					
Magnesium Stearate	NF, Ph.Eur.					
(b) (4) (b) (4)						
Dapagliflozin Propanediol[d] (b) (4)	In-house[e] NF, Ph.Eur.	Active (b) (4)				
Lactose Anhydrous	NF, Ph.Eur.					
Crospovidone	NF, Ph.Eur.					
(b) (4)	NF					
(b) (4)	NF, Ph.Eur.					
		(b) (4)				
(b) (4)	NA = Not Applicable					

Table 2. Tablet Film Coat Layers Used (sponsor's table)

Component	Quality Standard	Function	Quantity per Tablet (Dapa/Met XR mg/mg)			
			5/500	10/ 500	5/1000	10/ 1000
Film-Coating Layer						
(b) (4)						
Total Tablet Weight			1367.07	1367.07	1645.13	1645.13

(b) (4) NA = Not Applicable

Table 3. Composition of the Tablet Film Coat Layer (sponsor's table)

Strength (Dapa/Met XR mg/mg):		5/500	10/500	5/1000	10/ 1000
Component	Quality Standard	Orange (b) (4)	Pink (b) (4)	Pink (b) (4)	Yellow (b) (4)
Polyvinyl Alcohol- (b) (4)	USP, Ph.Eur.	(b) (4)			
Titanium Dioxide (b) (4)	USP, Ph.Eur.				
Polyethylene Glycol (b) (4)	NF, Ph.Eur.				
Talc (b) (4)	USP, Ph.Eur.				
Colorant					

* Values are shown in %w/w

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

Dapagliflozin: None
Metformin XR: None.

2.6 Proposed Clinical Population and Dosing Regimen

T2DM subjects treated once daily with dapagliflozin/metformin XR at 5/500, 5/1000, 10/500 and 10/1000 mg/mg.

(b) (4)

(b) (4)

The sponsor was also granted a waiver for the dapagliflozin monotherapy in the 0-9 year old children, as T2DM is not common in this age group. No additional, nonclinical toxicology studies are required to support the pediatric dapagliflozin monotherapy or FDC with metformin XR.

2.7 Regulatory Background

NDA's for dapagliflozin and metformin XR were approved by the FDA January 8th 2014 and October 13th 2000, respectively. The sponsor is seeking approval of once daily orally administered fixed dose combination (FDC) of dapagliflozin and metformin XR at four dosage strengths (dapa/met XR: 5/500, 5/1000, 10/500 and 10/1000 mg/mg). This NDA for the FDC was submitted to the Agency October 29th 2013 and relies primarily on the sponsor's approved NDA for dapagliflozin and letters of authorization for the DMF relating to metformin hydrochloride XR.

3 Studies Submitted

3.1 Studies Reviewed

Dapagliflozin (BMS-512148) and Metformin (BMS-207150) Three-Month Oral Combination Toxicity Study in Rats (Study# DN10008).

Dapagliflozin (BMS-512148) and Metformin (BMS-207150) Seven Day Oral Toxicokinetic Study in Rats (Study# DN09023).

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

NDA 202,293 (Dapagliflozin)
NDA 21,202 (Glucophage XR)
IND 106,890 (Dapagliflozin and metformin XR co-administered)

All other pharmacology/toxicology studies relevant to evaluation of Xigduo™ XR have been reviewed previously under NDA 202,293 for Farxiga (dapagliflozin) and under NDA 21,202 for Glucophage XR (metformin XR). Furthermore, the following dapagliflozin and metformin co-administered studies were reviewed under IND 106,890 and thus only a brief summary is provided for reference and labeling purposes (if applicable).

Dapagliflozin (BMS-512148) and Metformin (BMS-207150) Three-Month Oral Combination Toxicity Study in Rats (Study# DN10008).

Dapagliflozin (BMS-512148) and Metformin (BMS-207150) Seven Day Oral Toxicokinetic Study in Rats (Study# DN09023).

6 General Toxicology

6.2 Repeat-Dose Toxicity

General toxicity for the co-administered dapagliflozin and metformin was assessed in a 7-day repeat dose toxicokinetic study and a 3 month toxicology study, both in the rat. In the rat toxicokinetic study dapagliflozin was evaluated at 50 mg/kg either alone or in co-administered with metformin. Exposure to metformin was evaluated at 100, 300 or 600 mg/kg.

In the 3 month rat toxicology study exposure to dapagliflozin was evaluated at 1 or 5 mg/kg either alone or co-administered with metformin. Exposure to metformin was evaluated at 150 mg/kg.

All studies were fully reviewed under IND 106,890 and are summarized below.

Dapagliflozin (BMS-512148) and Metformin (BMS-207150) Seven Day Oral Toxicokinetic Study in Rats (Study# DN09023).

Dapagliflozin=d, metformin=m: 0(d)/100(m), 0(d)/300(m), 0(d)/600(m), 50(d)/0(m) and 50(d)/600(m) mg/kg

Key Study Findings

- The 7-day rat study was purely for toxicokinetics with minimal study observations conducted. Consequently, a NOAEL was not defined for the study.
- Exposure to dapagliflozin is slightly decreased in males when combined with metformin (exposure was 70% of the level seen in the absence of metformin).
- Exposure to metformin is unchanged when combined with dapagliflozin.
- Mean dapagliflozin exposure was 701x and 593x MRHD (10 mg dapagliflozin) for 50(d)/0(m) and 50(d)/600(m) mg/kg, respectively.
- Mean metformin exposure was 2x, 5x, 7x and 7x MRHD (2000 mg metformin XR) for 0(d)/100(m), 0(d)/300(m), 0(d)/600(m) and 50(d)/600(m) mg/kg, respectively.

Dapagliflozin (BMS-512148) and Metformin (BMS-207150) Three-Month Oral Combination Toxicity Study in Rats

Dapagliflozin=d, metformin=m: 0/0, 5(d)/0(m), 0(d)/150(m), 1(d)/150(m) and 5(d)/150(m) mg/kg

Key Study Findings

- Absolute kidney and kidney to body/brain weight ratios were slightly increased (1-1.3-fold) in all dapagliflozin treated groups but not in the metformin alone group. This change was without a pathology correlate.
- Vacuolation of the zona glomerulosa of the adrenal gland (minimal to slight) were observed with dapagliflozin alone and dapagliflozin in combination with metformin groups.
- Pharmacodynamic effects of dapagliflozin treatment alone or in combination with metformin were observed including: glucosuria, polyuria, calciuria and increased urinary sodium and phosphorus.
- There were no toxicologically adverse or toxicokinetic drug-drug interactions following the co-administration of dapagliflozin with metformin.
- Mean dapagliflozin exposure was 59x, 11x and 52x MRHD (10 mg dapagliflozin) for 5(d)/0(m), 1(d)/150(m) and 5(d)/150(m) mg/kg, respectively.
- Mean metformin exposure was 1x, 1x and 1x MRHD (2000 mg metformin) for 0(d)/150(m), 1(d)/150(m) and 5(d)/150(m) mg/kg, respectively.
- The NOAEL for dapagliflozin is 5 mg/kg (59x MRHD dapagliflozin, $AUC_{0\text{-}24h}$ = 465 ng.h/mL, 10 mg dapagliflozin) without metformin and 5/150 mg/kg with metformin (52x MRHD dapagliflozin, $AUC_{0\text{-}24h}$ = 465 ng.h/mL, 10 mg dapagliflozin, 1x MRHD metformin, AUC=26,667 ng.hr/mL, 2000 mg metformin XR).

11 Integrated Summary and Safety Evaluation

The sponsor is seeking the approval of dapagliflozin as a fixed dose combination (FDC) with metformin extended release (Xigduo™ XR). Dapagliflozin is a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), approved by the FDA January 8th 2014. Metformin extended release (XR) is a biguanide class insulin sensitizer antihyperglycemic agent approved by the FDA October 13th 2000.

Non-clinical studies with the fixed-dose combination (FDC) were not performed. Toxicity unique to the combination of dapagliflozin and metformin was evaluated in rats co-administered each drug separately and in combination in a rat 7-day toxicokinetic (TK) study and for up to three months in a rat toxicology study.

All nonclinical studies were conducted using the oral administration of the drug, which is the clinical route of exposure. With the exception of the 7-day rat TK study, all studies were conducted in accordance with US FDA GLP regulation (21 CFR58) as stated by the sponsor.

Dapagliflozin exerts its pharmacological activity by inhibiting SGLT2, the major transporter responsible for renal glucose absorption. By inhibiting renal glucose reabsorption, the urinary excretion of glucose is enhanced, thereby reducing fasting and

postprandial glucose levels, in a mechanism that is independent of insulin. There is extensive nonclinical experience with dapagliflozin that has been reviewed under NDA 202,293.

Metformin hydrochloride is a biguanide class drug that lowers both basal and postprandial glucose by decreasing hepatic glucose production and intestinal glucose absorption. Metformin also improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin was approved for use in the USA in 1995 and metformin extended release (XR) was approved in 2000. Thus, there is extensive clinical experience for the use of metformin in T2DM adults and children.

Pivotal toxicology studies with co-administered drugs were conducted to bridge potential toxicity of the combination treatment of dapagliflozin and metformin XR. In the 7-day oral toxicokinetic study in the rat, treatment with metformin alone or co-administered with dapagliflozin does not alter metformin exposure. Exposure to dapagliflozin was slightly decreased in male rats when co-administered with metformin (exposure was 70% of the level seen in the absence of metformin).

In the 3 month rat study, the combination of dapagliflozin and metformin when co-administered did not result in adverse toxicological or toxicokinetic drug-drug interactions.

The following summary is taken from the pharmacology/toxicology review for dapagliflozin written for NDA 202-293.

Pharmacology
Dapagliflozin (BMS-512148 or Farxiga™) is a selective inhibitor of sodium glucose co-transporter (SGLT) 2. SGLT2 is selectively expressed in the kidney S1 proximal tubule and is responsible for the majority (90%) of the renal reabsorption of glucose. Inhibition of SGLT2 by dapagliflozin results in the excretion of glucose thereby producing glucosuria. In in vitro studies dapagliflozin was a potent and selective inhibitor of human (h) SGLT2 relative to the closely related hSGLT1 with a selectivity of 1242-1600-fold. In nonclinical models of diabetes dapagliflozin promoted glucose excretion, polyuria and lowered plasma glucose in diabetic and non-diabetic animal models under conditions of hyperglycemia (oral glucose tolerance test).

Safety pharmacology assessment of cardiovascular, neurological and pulmonary effects of dapagliflozin did not identify significant liabilities.

Absorption, Distribution, Metabolism and Excretion
An oral dose of dapagliflozin was rapidly absorbed and is approximately 80% bioavailable in the rat and dog but only 25% bioavailable in the non-human primate. Dapagliflozin distributes rapidly to most rat tissues with low amounts distributing to the brain and bone. The steady state volume of distribution for dapagliflozin was greater than that of plasma suggestive of extravascular distribution. Dapagliflozin has a longer half-life in humans (13 hours) than in the rat, monkey or dog (3-7 hours), suggestive of

different rates of renal elimination. Plasma protein binding was high (91-95%) in humans and in all nonclinical species.

Dapagliflozin undergoes low (10%) oxidative metabolism in vitro by numerous human cytochrome P450 enzymes. The major metabolites in hepatocyte preparations were the glucuronide conjugates and dapagliflozin 3-O-glucuronide was the major human metabolite formed in the kidney and also the liver. UGT1A9 was the major human UDP-glucuronosyltransferase responsible for the formation of the inactive dapagliflozin 3-O-glucuronide and this enzyme is predominantly found in the kidney. No unique dapagliflozin human metabolites were identified. Dapagliflozin excretion is predominately via metabolism to the dapagliflozin 3-O-glucuronide followed by excretion in the urine. The parent is also found to a much lower extent in the urine, feces and bile. Dapagliflozin was also found to be excreted in the milk of lactating rats.

Dapagliflozin was a weak substrate for p-glycoprotein and did not inhibit OAT1 or OCT2 and was weak inhibitor of hOAT3. These results suggest a low probability for drug-drug interactions except for potential inducers/inhibitors of UGT1A9 which may affect the elimination of dapagliflozin.

General Toxicology
Pivotal repeat dose studies were conducted in the Sprague-Dawley rat and Beagle dogs up to 6 and 12 months duration, respectively. In the rat the dapagliflozin exposure was 83-3097x MRHD and in the dog the exposure was 128x-3312x MRHD. Findings in the pivotal rat and dog studies were generally consistent with pharmacodynamic activity of dapagliflozin, including dose-dependent increases in urinary glucose. The toxicological profile of dapagliflozin supported the doses and duration of clinical studies conducted throughout drug development. At clinically relevant drug exposure, pharmacodynamic action also resulted in reduced body weight (BW), increased food consumption (FC), increased urinary volume, calcium (Ca), phosphorus, protein and decreased urinary osmolality.

In the 6 month rat study major target organs with toxicity included the kidney (chronic progressive nephropathy (CPN), mineral deposits, tubule epithelial hyperplasia and urothelial hyperplasia), sternum and femur (increased trabecular bone), heart, vessels and trachea (mineralization), adrenal glands (vacuolation/hypertrophy) and spleen and liver (extramedullary hematopoiesis). The target organs identified were likely the result of exaggerated pharmacology due to inhibition of SGLT2 (e.g. glucosuria) or were the result of off-target effects or were due to the osmotic and/or diuretic effect of enhanced glucose excretion (e.g. polyuria). Adrenal gland vacuolation could be a compensatory response of aldosterone production due to increased sodium excretion. Off-target effects include the increased trabecular bone and tissue mineralization, likely due to modulation of calcium homeostasis and increased urinary calcium excretion. The propensity for dapagliflozin to cause off-target inhibition of SGLT1 in humans is reduced due to the lower affinity of dapagliflozin for human SGLT1 compared to the rat. Overall, target organ toxicities in adult rats occurred at high exposure multiples (≥3097x MRHD) and the safety margins to the final clinical dose are high suggesting low clinical risk.

Reproductive Toxicology
Reproductive and developmental toxicity were assessed in fertility, early embryonic development, pre- and post-natal development and juvenile animal studies. In the fertility study no effects were seen on mating and fertility indices in the females and the males, except for altered spermatogenesis at 1707x MRHD. Resorptions were increased in females at the high dose (188x MRHD), resulting in a NOAEL for this finding of 38x MRHD. No effects were seen on mating and fertility indices in the females and a NOAEL for female fertility was 188x MRHD due to reduced weight gain at higher doses

Dapagliflozin was not teratogenic at up to 75 mg/kg (1141x MRHD) in the rat. Higher exposures resulted in late gestational fetal deaths and malformations and skeletal variations at ≥ 1141x MRHD. Dapagliflozin was also not teratogenic in the rabbit at up to 184x MRHD and effects on the litters, malformations and variations were not observed.

Exposure to dapagliflozin at 19-1415x MRHD in a pre- and post-natal development study in the rat had no pathological effects in the dams, yet showed renal pelvic dilatation at the high dose in the in utero and lactationally exposed pups (1415x MRHD). Due to reduced growth in the pups the NOAEL was <19x MRHD. In the dams the NOAEL was 249x MRHD due to reduced body weight gain at the high dose. Treatment of juvenile rat pups until maturity replicated the renal pelvic dilatation pathology but at drug exposure that is potentially clinically relevant, and also showed irreversibility in recovery animals, suggesting dapagliflozin is a renal pelvic development toxicant.

Genetic Toxicology
Dapagliflozin was not mutagenic or clastogenic in an in vitro Ames assay or in the in vivo assays: rat bone marrow micronucleus assay or peripheral blood lymphocyte chromosomal aberration assay or the hepatocyte unscheduled DNA synthesis (UDS) assay. However, dapagliflozin was clastogenic in the presence of S9 in multiple in vitro chromosomal aberration assays. The necessity of S9 (rat liver microsomes) to elicit clastogenicity indicates that an unidentified metabolite or metabolites of dapagliflozin were causative, not the intact parent molecule. However, all metabolites of dapagliflozin identified in human subjects have also been identified in mice and rats *in vivo*, and have been evaluated for genotoxic potential in nonclinical studies. The weight of evidence supports the view that dapagliflozin and its identified metabolites are unlikely to be clastogenic in human subjects.

Carcinogenicity
Dapagliflozin was assessed for its potential to induce tumors in two-year bioassays conducted in rats and mice. The two-year bioassays are intended to detect drug-induced tumors that arise from genotoxic as well as non-genotoxic mechanisms of action after approximately life-time exposure to an investigational drug. Dapagliflozin did not increase the incidence of any tumor in rats and mice at drug exposures reaching 131x and 72x the clinical dose, respectively.

Special Toxicology Studies
Exposure of rats in utero and during lactation to dapagliflozin at 16x to 918x MRHD resulted in excretion of dapagliflozin in the breast milk of lactating rats at a milk to plasma ratio of 0.49x. The fetal exposure to dapagliflozin was 2-142x MRHD, suggesting that pups were exposed to pharmacologically and toxicologically relevant levels of the drug.

The toxicity of metformin is well characterized and clinically manifests as lactic acidosis and gastrointestinal side effects (e.g. diarrhea, bloating and discomfort). Based on nonclinical toxicity studies conducted with the dapagliflozin monotherapy, dapagliflozin is not expected to exacerbate the aforementioned clinical metformin toxicities. For the co-administered dapagliflozin and metformin, the observed nonclinical toxicity in the three month rat study resulted in minimal to slight adrenal vacuolation. This was considered non-adverse, and was driven by a secondary pharmacodynamic response to dapagliflozin, at high exposure multiples of 59x dapagliflozin MRHD. The 59x dapagliflozin MRHD was the high dose and was also considered the NOAEL, thus giving a wide clinical margin to the observed toxicity.

Metformin is excreted unchanged in the urine and renal impairment leads to increased metformin exposure through decreased urinary excretion. Increased metformin exposure increases the risk of lactic acidosis, a rare clinical adverse event. The efficacy of dapagliflozin also requires a functioning kidney and dapagliflozin is contraindicated in patients with moderate to severe renal impairment. The dapagliflozin/metformin FDC proposed label also carries the same contraindication. Chronic exposure to dapagliflozin at high exposure multiples (>500x MRHD) results in hyperplastic/degenerative kidney changes in the rat and dog. The NOAEL for these histopathological changes was 300x and 500x dapagliflozin MRHD, in the rat and dog, respectively.

Overall, the co-administration of dapagliflozin with metformin was consistent with toxicological findings observed in pivotal nonclinical toxicology studies with the dapagliflozin monotherapy and did not result in new adverse findings.

Potential safety issues relevant to the clinical use of dapagliflozin in combination with metformin are summarized here:

1. Hypoglycemia risk is expected to be low due to the insulin-independent mechanism of dapagliflozin's pharmacological action. Hypoglycemia was not observed in the 3 month rat dapagliflozin and metformin co-administration study despite high dapagliflozin exposure multiples (59x MRHD).

2. Both dapagliflozin and metformin are secreted in the milk of nursing rats. It is unknown if metformin or dapagliflozin are excreted in human milk. No nonclinical studies with the FDC or co-administered drugs in nursing or lactating animals have been conducted. However, the sponsor acknowledges the developmental risk of using dapagliflozin during nursing and the Xigduo™ XR label appropriately conveys the risk.

Table 4. Summary of Three Month Rat Toxicology Study

Rat, 3 months dapagliflozin and metformin co-administration 0/0, 5/0, 0/150, 1/150 And 5/150 mg/kg/day	NOAEL (dapa/ metformin)	Multiple of Dapagliflozin MRHD*	Multiple of Metformin MRHD#
Adverse Effect: None.	5/0 mg/kg	M: 50x F: 68x Mean: 59x	NA
	5/150 mg/kg	M:43x F: 60x Mean: 52x	M:1x F: 1x Mean: 1x

*AUC in human: 0.465 ng.hr/ml at 10 mg/day dapagliflozin. NA – not applicable
#AUC in human: 26,667 ng.hr/ml at 2000 mg/day metformin XR.

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/s/

MUKESH SUMMAN
06/11/2014

RONALD L WANGE
06/11/2014
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205649 **Applicant: Bristol Myers Squibb/ AstraZeneca (BMS/AZ)** **Stamp Date: October 29th 2013**

Drug Name: Dapagliflozin/Metformin XR FDC **NDA Type: 505(b)1**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		Oral dose administration (gavage for animal studies and tablets in the clinic)
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		

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8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Pharmacology/Toxicology labeling is in accordance with 21CFR.201.57. Human dose equivalents are expressed as MRHD multiples.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?		X	Dapagliflozin/Metformin XR FDC abuse potential studies were not carried out.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. Dapagliflozin/Metformin XR FDC is a new molecular entity that will not be marketed OTC.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES___X___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

MUKESH SUMMAN
12/10/2013

TODD M BOURCIER
12/10/2013
pharm/tox supports filing