



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for Dapagliflozin (as propanediol monohydrate) / Metformin hydrochloride

Proprietary product names: Xigduo XR 10/500,  
Xigduo XR 10/1000, Xigduo XR 5/1000

Sponsor: AstraZeneca Pty Ltd

**December 2014**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

## About AusPARs

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration curve
AUC <sub>(INF)</sub>	Area under the curve extrapolated to infinity
AUC <sub>(0-T)</sub>	Area under the curve extrapolated from time zero to the time of the last quantifiable concentration
BA	Bioavailability
BE	Bioequivalence
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use, formerly known as the Committee for Proprietary Medicinal Products (CPMP)
CI	Confidence interval
C <sub>max</sub>	Maximum plasma drug concentration
CrCl	Creatinine clearance
CSR	Clinical study report
CV	Cardiovascular
Dapa/Met	Dapagliflozin/Metformin
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (USA)

Abbreviation	Meaning
FDC	Fixed dose combination
FPG	Fasting plasma glucose
h	hour/s
HbA1c	Glycated haemoglobin
HCl	Hydrochloride
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Immediate release
mg	Milligram
mL	Millilitre
OAD	Oral antidiabetic drug
PI	Product Information
PK	Pharmacokinetic/s
PPG	Postprandial glucose
PT	Preferred term
RMP	Risk Management Plan
SAE	Serious adverse event
SGLT2	Sodium dependent glucose co-transporter 2
T2DM	Type 2 diabetes mellitus
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
UTI	Urinary tract infection
US	United States
XR	Extended release
µg	Microgram

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Fixed dose combination
<i>Decision:</i>	Approved
<i>Date of decision:</i>	11 July 2014
<i>Active ingredients:</i>	Dapagliflozin (as propanediol monohydrate) and metformin hydrochloride (HCl)
<i>Product names:</i>	Xigduo XR 10/500, Xigduo XR 10/1000, Xigduo XR 5/1000
<i>Sponsor's name and address:</i>	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
<i>Dose form:</i>	Modified release <sup>1</sup> tablet
<i>Strengths:</i>	Dapagliflozin (as propanediol monohydrate)/metformin HCl: 10 mg/500 mg, 10 mg/1000 mg, and 5 mg/1000 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	7 and 28 (10/500 or 10/1000 strengths); 14 and 56 (5/1000 strength)
<i>Approved therapeutic use:</i>	<i>Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate (see Clinical Trials and Precautions for available data on the combination therapy).</i>
<i>Route of administration:</i>	Oral
<i>Dosage (abbreviated):</i>	The dosage of antihyperglycaemic therapy with Xigduo XR should be individualised on the basis of the patient's current regimen, effectiveness, and to tolerability while not exceeding the maximum recommended dose of dapagliflozin 10 mg and metformin extended release 2000 mg (see Product Information at Attachment 1 for full <i>Dosage and Administration</i> )
<i>ARTG numbers:</i>	211294, 211295, 211296

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<sup>1</sup> The modified release aspect relates to the metformin HCl component only; the release of dapagliflozin from the tablets is immediate.

## Product background

Dapagliflozin is an inhibitor of renal sodium dependent glucose co-transporter 2 (SGLT2) and was registered as dapagliflozin (propanediol monohydrate) 10 mg tablets (Forxiga) in October 2012 for the treatment of patients with type 2 diabetes mellitus (T2DM)<sup>2</sup>. Forxiga is used as monotherapy or in combination with other oral antidiabetic drugs (OADs) such as metformin.

Metformin is a biguanide OAD and has been available for the treatment of patients with T2DM for more than 20 years, either as monotherapy or in combination with other OADs.

This AusPAR describes the application by the AstraZeneca Pty Ltd (the sponsor) to register fixed dose combination (FDC) tablets containing dapagliflozin (as propanediol monohydrate) and metformin HCl for the following indication:

*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.*

The metformin HCl component of the tablets is an extended release (XR) form, while the dapagliflozin (as propanediol monohydrate) component is an immediate release form. The following FDC strengths are proposed:

- 10 mg dapagliflozin (as propanediol monohydrate) and 500 mg metformin HCl (Xigduo XR 10/500);
- 10 mg dapagliflozin (as propanediol monohydrate) and 1000 mg metformin HCl (Xigduo XR 10/1000); and
- 5 mg dapagliflozin (as propanediol monohydrate) and 1000 mg metformin HCl (Xigduo XR 5/1000).

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 18 July 2014.

At the time the TGA considered this application, an application had been approved in the European Union (16 January 2014) for an immediate release presentation of the fixed dose combination.

## Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

## II. Quality findings

### Introduction

The sponsor seeks registration of new FDC, modified release, film coated tablets containing 10/500 mg, 10/1000 mg and 5/1000 mg of dapagliflozin/metformin HCl. Although the tablets are labelled in terms of free dapagliflozin, the dapagliflozin is added

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<sup>2</sup> The AusPAR for dapagliflozin Forxiga 10 mg tablets (PM-2012-03812-3-5) is available at: <<http://www.tga.gov.au/auspar/auspar-dapagliflozin-propanediol-monohydrate-4>>



to the tablets as dapagliflozin propanediol monohydrate. Conversely, the labelled amounts of metformin in the tablets refer to the amounts of metformin HCl present.

Dapagliflozin is a synthetic aryl glycoside registered in Australia in 2012 for use in 10 mg Forxiga immediate release tablets.

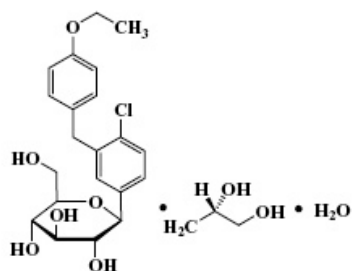
Metformin HCl is a biguanide antidiabetic agent that is a well characterised compendial drug. Metformin immediate release and modified tablets are registered in Australia by a number of companies. The innovator extended release product (Diabex XR) is available in 500 mg, 750 mg and 1000 mg strengths.

## Drug substance (active ingredient)

### Dapagliflozin

The dapagliflozin propanediol monohydrate (structure shown below) is a solvate form containing a 1:1:1 ratio of dapagliflozin, (S)(+)-1, 2-propanediol and water. The drug substance is a white to off white non-hygroscopic powder. The aqueous solubility is 2.1 mg/mL over the pH range 1.2-6.8 and the absolute bioavailability in humans is 78%. It is a Biopharmaceutics Classification System (BCS) class III compound.

**Figure 1: Structure of dapagliflozin propanediol monohydrate**

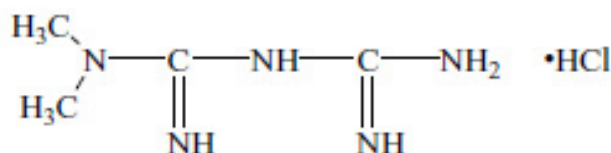


The drug substance manufacture, quality control and stability have been assessed (and approved) as part of the previous application to register Forxiga (PM-2012-03812-3-5).

### Metformin hydrochloride

Metformin HCl (structure shown below) is a white to off-white crystalline solid. It is freely soluble in water, slightly soluble in alcohol and practically insoluble in acetone and dichloromethane. Based on its aqueous solubility and permeability it is classified as a BCS class III compound (high solubility/ low permeability).

**Figure 2: Structure of metformin HCl**



Metformin HCl manufacture, quality control and stability aspects of the drug substance manufacture have been assessed and accepted by the TGA.

## Drug product

The quality of the tablets is controlled by specifications that include appropriate tests and limits for assay (dapagliflozin and metformin), impurities, dissolution as well as water and microbial content. Appropriate justification was provided for not routinely monitoring dapagliflozin impurities.

The specification test methods have been adequately described and validated.

A common dissolution method was developed for both the immediate release dapagliflozin and extended release metformin. The limits applied to dapagliflozin and metformin are appropriate.

Stability data have been generated under stressed, accelerated and real time conditions. These data support the proposed shelf life of 24 months, when the product is stored in its proposed blister packaging at below 30°C.

## Biopharmaceutics

The key biopharmaceutic studies are summarised briefly below.

- Studies MB102092 and MB102100 demonstrated (under fed conditions) bioequivalence between the proposed 10/1000 mg and 5/500 mg tablets relative to individual dapagliflozin and US sourced metformin XR tablets (Glucophage XR). These studies also established the effect of food on the pharmacokinetics (PK) of the proposed FDCs and characterised their steady state PK.
- Study MB102125 demonstrated the steady state (under fed conditions) bioequivalence of the proposed 10/1000 mg and 5/500 mg tablets relative to the co-administration of the individual components of dapagliflozin and Australian sourced Diabex XR tablets.
- Justification was supplied for not conducting bioequivalence studies on the proposed 5/1000 mg tablets. The chemistry aspects of this justification are considered acceptable.

## Advisory committee considerations

No major issues were found with the submission and it did not require consideration by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

## Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and biopharmaceutics.

# III. Nonclinical findings

## Introduction

The nonclinical data consisted of a preliminary 7 day toxicokinetic study and a 3 month repeat dose toxicity study in rats with the dapagliflozin/metformin combination. The composition of the submitted package is consistent with the relevant EU guideline,

EMA/CHMP/SWP/258498/2005 *Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products.*

## Pharmacology

No nonclinical efficacy studies with the proposed combination were submitted.

## Pharmacokinetics

Based on studies with cytochrome P450 (CYP450) enzymes and transporters, dapagliflozin is not expected to alter the PK of co-administered drugs (studies reported in the TGA previous evaluation of dapagliflozin as a new chemical entity). In human subjects, dapagliflozin is metabolised predominantly by uridine diphosphate glucuronosyltransferase (UGT1A9). No information was provided regarding the effect of metformin on UGT1A9 activity or expression. However, compared with monotherapy, there was no effect on the exposure of metformin or dapagliflozin when provided in combination to rats. Furthermore, it is stated in the PI document for dapagliflozin that, in human subjects, co-administration of dapagliflozin and metformin has no effect on the PK of the other drug. Therefore, there appears to be no clinically-relevant PK drug interactions with dapagliflozin and metformin.

## Toxicology

The repeat dose toxicity study of the dapagliflozin/metformin combination was of 3 months duration. This is consistent with the EU guideline on the non-clinical development of fixed combinations of medicinal products (EMA/CHMP/SWP/258498/2005). Based on pharmacological considerations, rats were considered an appropriate species to assess the toxicity of dapagliflozin (studies in the TGA previous evaluation of dapagliflozin as a new chemical entity). However, there are some limitations with the use of rats with respect to PK parameters. The inactive metabolite, dapagliflozin 3-O-glucuronide, is found at higher levels than dapagliflozin in human plasma (exposures were 183% those of the parent drug), while this is only a minor metabolite in rats (exposures 0.36% those of the parent drug in plasma). The higher glucuronide formation in human subjects, affects the excretion pattern with urinary excretion predominant in humans and drug-related material excreted in both the urine and faeces in rats. Nonetheless, rats are a species that have been used previously to assess the toxicity of dapagliflozin. This species has also been used to assess the toxicity of other metformin combination drugs. The dose ratios of dapagliflozin/metformin (base) used in the study (1:30–1:150) were similar to those proposed clinically (1:39–1:156), but the ratio of dapagliflozin area under the concentration-time curve (AUC) to metformin AUC was significantly different to that seen clinically, probably as a result of the greater metabolism of dapagliflozin (to dapagliflozin 3-O-glucuronide) in human subjects. Parallel single agent control groups were used.

Clinical PK data were not available for the maximum dose (10 mg/2000 mg dapagliflozin/metformin HCl); therefore, relative exposure comparisons were calculated using the AUC<sub>0-24h</sub> for the individual components; 0.438 µg.h/mL for 10 mg dapagliflozin and 20.5 µg.h/mL for a 2000 mg dose of metformin HCl XR<sup>3</sup>. Exposures to dapagliflozin were significantly higher than those expected clinically (exposure ratio based on AUC (ER<sub>AUC</sub>) 12–63) but exposures to metformin were relatively low (ER<sub>AUC</sub> 1.5–2), which probably explains the absence of any metformin associated toxicities in the submitted study. In 3 month rat studies to support other FDCs with metformin, higher metformin

<sup>3</sup> Timmins P., Donahue S., Meeker J. and Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin Pharmacokinet* 2005;44:721–729.

doses have been used (up to 1000 mg/kg/day PO; vildagliptin [Galvumet AusPAR]) and the no observed adverse effect level (NOAEL) in rats has been reported to be 200 mg/kg/day PO metformin<sup>4</sup>. Therefore, the chosen metformin dose of 150 mg/kg/day is considered too low. Given the dominant contribution of dapagliflozin to toxicity findings, a higher metformin dose and a more clinically relevant dapagliflozin:metformin exposure level would have been desirable. Furthermore, exposures to the main human metabolite of dapagliflozin, dapagliflozin 3-O-glucuronide, in the submitted study are estimated to be extremely low;  $\leq 12\%$  of the clinical exposure<sup>5</sup>.

**Table 1: Relative exposure in repeat-dose toxicity study**

Species; study duration	Dose (mg/kg/day)		AUC <sub>0-24 h</sub> (µg.h/mL)		Exposure ratio	
	Dapa	Met	Dapa	Met	Dapa	Met
Rat (SD) 13 weeks <sup>a</sup>	1	150	5.19	32.6	12	1.6
	5	150	24.1	28.7	55	1.4
	5	0	27.5	–	63	–
	0	150	–	38.5	–	1.9
Human	[10 mg]	[1560 mg] <sup>b</sup>	0.438 <sup>c</sup>	20.5 <sup>d</sup>	–	–

Dapa = dapagliflozin. Met = metformin. a Combined male and female data from Week 13; b corresponding to  $2 \times 1000$  mg metformin HCl; c data from previous TGA evaluation report; d data from Timmins et al. (2005)

Clinical chemistry (decreased glucose levels) and urinalysis changes (glucosuria, osmotic diuresis, hypercalciuria and natriuresis) seen in animals given dapagliflozin (5 mg/kg/day orally) were generally similar to those reported previously and are consistent with the pharmacological action of dapagliflozin. The increased kidney weight seen in dapagliflozin treated animals is likely to be associated with the significantly increased urinary output and workload associated with the elimination of increased amounts of glucose. The only other notable post mortem finding in dapagliflozin treated rats was an increase in the incidence and severity (to slight) of vacuolation of the zona glomerulosa of the adrenal gland, likely secondary to the electrolyte changes as a result of the diuretic effect and a compensating increase in aldosterone levels.

Aside from some minor changes in clinical chemistry parameters, there were no significant drug-associated findings in metformin-only treated animals (150 mg/kg/day orally).

There were no new or unexpected toxicities observed in animals given dapagliflozin/metformin (5/150 mg/kg/day dapagliflozin/metformin). The clinical chemistry and urinalysis changes, the increase in kidney weights and adrenal gland histological findings in the combination group, were of a similar incidence and magnitude to that observed in the dapagliflozin-only group.

However, as mentioned previously, the metformin doses are considered low. Higher metformin doses and dose ratios resulting in a more clinically-relevant dapagliflozin:metformin exposure level should have been considered. Given the

<sup>4</sup> Quaille M.P., Melich D.H., Jordan H.L., Nold J.B., Chism J.P., Polli J.W., Smith G.A. & Rhodes M.C. Toxicity and toxicokinetics of metformin in rats. *Toxicol. Appl. Pharmacol.* 2010:243;340–347.

<sup>5</sup> Based on a human AUC<sub>0-24 h</sub> of 0.803 µg.h/mL, with the AUC<sub>0-24 h</sub> for dapagliflozin 3-O-glucuronide being 0.36% of the dapagliflozin AUC<sub>0-24 h</sub> in rats.

limitations in the study design, no firm conclusions can be drawn from the negative findings in this study. Previous toxicity studies with dapagliflozin and metformin as individual components at higher doses indicated the adrenal gland and the kidney as shared target organs for toxicity and a risk for metabolic acidosis exists with both compounds (Quaile et al., 2010). While no definitive conclusions can be drawn regarding the toxicity of the combination due to the limitations in the submitted study, this should not preclude registration, given that the two drugs are already approved for use in free combination. However, given both compounds target the same organs, a more appropriately designed toxicity study should be conducted to assess the potential long term effects of dapagliflozin/metformin on the adrenal glands and the kidneys.

### Nonclinical summary and conclusions

- No animal studies were submitted to support the efficacy of the proposed combination.
- No PK interactions were observed in rats with co-administration of dapagliflozin/metformin.
- One repeat dose toxicity study of 3 months duration was submitted in Module 4. While no new or unexpected toxicities were seen in rats treated with the combination of dapagliflozin/metformin, the poor choice of doses in the study limits the interpretation of the negative findings. No firm conclusions can be drawn from this study.
- The absence of an adequate combination toxicity study should not preclude registration, given that the drugs are already approved for use in free combination at the doses and indication sought here.

Revisions to nonclinical statements in the PI were recommended. Details of these are beyond the scope of the AusPAR.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

This is a full submission to register a new fixed combination product consisting of dapagliflozin, which is a reversible competitive inhibitor of SGLT2, and metformin, a biguanide, which is an OAD. The proposed indication is:

*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.*

The submission proposes registration of the following dosage forms and strengths:

- Xigduo XR (dapagliflozin/metformin HCl extended-release) 10 mg/500 mg tablets
- Xigduo XR (dapagliflozin/metformin HCl extended-release) 10 mg/1,000 mg tablets
- Xigduo XR (dapagliflozin/metformin HCl extended-release) 5 mg/1,000 mg tablets

**Evaluator's comment:** The submission also includes the following strength: 5 mg dapagliflozin/500 mg metformin HCl extended-release) 5 mg/500 mg tablets.

The sponsor's summary states "As dapagliflozin 10 mg once daily is the only recommended dose of dapagliflozin in Australia, the 5 mg/500 mg dapagliflozin/metformin XR FDC will not be marketed. The remaining 3 dose strengths will allow once daily dosing of dapagliflozin with metformin XR to achieve a total daily dose of 10 mg dapagliflozin and 500 mg, 1000 mg or 2000 mg metformin XR."

### Clinical rationale

Type 2 diabetes mellitus is a chronic disease characterised by hyperglycaemia and an increased risk of microvascular and macrovascular complications. An important goal of diabetes care is to achieve adequate glycaemic control in order to reduce long term complications caused by chronic hyperglycaemia. Despite the well documented benefits of adequate glycaemic control and the availability of many approved medications for the treatment of T2DM, glycaemic control rates remain poor. Moreover, T2DM is often accompanied by other conditions that affect morbidity and mortality, including hypertension, obesity, and dyslipidaemia.

Many patients with T2DM do not achieve satisfactory glycaemic control with a single, initial OAD such as metformin, and there is a need for effective combination therapy options in patients failing metformin treatment. The combination of dapagliflozin and metformin, through complementary mechanisms of action, represents a clinically relevant treatment to improve glycaemic control in patients with T2DM when treatment with both dapagliflozin and metformin is appropriate, including initial combination therapy, or in combination with other OADs or insulin.

Dapagliflozin was the first in a new class of compounds that inhibits the renal SGLT2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin is a potent, highly selective and orally active inhibitor of human SGLT2. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose which causes glucuresis, the urinary excretion of glucose, and this mechanism results in improved glycaemic control. In addition to the improved glycaemic control, the loss of calories with urinary glucose excretion leads to a decrease in body weight, mostly due to loss of fat. The increase in diuresis volume and urinary sodium loss associated with glucuresis reflects the diuretic property of dapagliflozin, and this mechanism is associated with moderate blood pressure (BP) reductions. Furthermore, due to its insulin independent mechanism of action, dapagliflozin is associated with a low risk of hypoglycaemia.

Dapagliflozin has been approved as an effective treatment that offers glycaemic control in a wide spectrum of patients with T2DM (as monotherapy; add-on to combination therapy with metformin, a sulphonylurea (SU), or insulin (alone or with one or both of metformin or an SU); or initial combination therapy with metformin) across a broad range of HbA1c. Dapagliflozin's mechanism of action is complementary to most other glucose lowering drugs.

Metformin HCl (metformin) is a well characterised OAD which has been in widespread use for decades and is the first-line agent of choice for T2DM. Metformin lowers HbA1c, FPG, and PPG concentrations in patients with T2DM, improving glycaemic control by reducing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilisation.

The dapagliflozin/metformin XR FDC product offers a simplification and convenience of therapy, with once daily administration with (or after) the evening meal, thereby improving patient compliance.

## Guidance

The TGA has adopted the following guidance documents related to this product:

- Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus CPMP/EWP/1080/00 30 May 2002, adopted by TGA 23 October 2002
- Guideline on clinical development of fixed combination medicinal products CPMP/EWP/240/95 Rev 1, adopted by TGA May 2010

## Contents of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

Module 5:

- 7 clinical pharmacology studies, including 3 that provided bioavailability data and 4 that provided bioequivalence data
- 7 efficacy/safety studies (all have been previously evaluated)
- 1 efficacy/safety study providing additional efficacy and safety data

Module 2:

- Clinical Overview, Summary of Biopharmaceutics, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references

## Paediatric data

The submission did not include paediatric data.

## Good clinical practice

Clinical Study reports (CSR) state that all studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements. The study protocols and informed consent documents were submitted to appropriate ethics committees and all patients and healthy subjects provided informed consent prior to enrolment to the studies.

## Pharmacokinetics

### Studies providing pharmacokinetic data

The sponsor provided only bioavailability and bioequivalence studies in this submission (Table 2). No additional specific clinical pharmacology studies were conducted for this submission. The applicant considered that sufficient PK data on dapagliflozin was submitted in the original application.

A 2-way drug-drug interaction study (MB102026<sup>6</sup>) between dapagliflozin and metformin was submitted in the initial dapagliflozin application and has shown no clinically meaningful effect of dapagliflozin on metformin PK and vice versa.

**Table 2: Submitted pharmacokinetic studies**

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	Bioavailability (BA)	MB102060	BA: met XR versus Glucophage XR
		MB102065	BA: FDC dapa/met XR versus Glucophage XR
		MB102071	BA: FDC dapa/met XR versus Glucophage XR
	Bioequivalence† (BE) - Single dose	MB 102092	BE: FDC dapa/met versus dapa + Glucophage XR
		MB 102100	BE: FDC dapa/met versus dapa + Glucophage XRL: effect of food
		CV181120	BE: Glucophage versus Diabex
	Bioequivalence† - Multi dose	MB 102092	BE: FDC dapa/met versus dapa + Glucophage XR
		MB102125	BE: FDC dapa/met versus dapa + Diabex XR
		MB 102100	BE: FDC dapa/met versus dapa + Glucophage XRL: effect of food
	Food Effect	MB 102100	BE: FDC dapa/met versus dapa + Glucophage XR: effect of food
		CV181120	BE: Glucophage versus Diabex
	PK in target patient population	Timing of dosing	MB102013b

Dapa = dapagliflozin; met = metformin. † Bioequivalence of different formulations.

None of the PK studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacokinetics

Given the lack of any clinical studies with the FDC tablets, the approval of the product rests largely with the bioequivalence studies.

<sup>6</sup> Evaluated in the original submission for dapagliflozin, PM-2010-03812-3-5



The Australia-specific pivotal bioequivalence study (MB102125) was conducted in order to ensure patients switching from Diabex XR will have an equivalent systemic exposure to metformin from the dapagliflozin/metformin XR FDCs. A steady-state, fed (high fat meal) bioequivalence study that used 5 mg or 10 mg dapagliflozin and 500 mg or 1000 mg Australian-sourced Diabex XR as the reference products and the 5 mg/500 mg XR and 10 mg/1000 mg XR dapagliflozin/metformin FDCs as test products was conducted. The results showed that both the 5 mg/500 mg and 10 mg/1000 mg dapagliflozin/metformin XR FDC formulations were bioequivalent to their individual components administered together (that is, the 90% confidence intervals (CIs) of the ratios of geometric least square means for dapagliflozin and metformin maximum concentration ( $C_{max}$ ),  $AUC_{(0-T)}$ , and  $AUC_{(INF)}$ , were entirely contained within 0.80 to 1.25). Therefore, Australian patients switching to the dapagliflozin/metformin XR FDCs from the same strengths of dapagliflozin + Diabex XR can be expected to have equivalent systemic exposures to both analytes from the FDCs. Likewise, patients taking Diabex XR who are adding dapagliflozin to their treatment regime can be expected to have equivalent systemic exposures to metformin from the dapagliflozin/metformin XR FDCs.

For both dapagliflozin and metformin, the results from the two supporting bioequivalence studies (MB102092 and MB102100) demonstrated bioequivalence of a 5/500 mg and 10/1000 mg dapagliflozin/metformin XR FDC tablet relative to co-administered individual component tablets (in these trials using US sourced Glucophage XR metformin) in fed healthy subjects.

When both the 5/500 mg and 10/1000 mg dapagliflozin/metformin XR FDC tablets were compared in the fasted and fed state, a light-fat meal decreased the  $C_{max}$  of dapagliflozin by about 34%, but did not affect  $AUC_{(0-T)}$  and  $AUC_{(INF)}$ . Based on the results seen in the dapagliflozin monotherapy development programme, as the cumulative (daily) amount of glucose excreted in the urine induced by dapagliflozin is dependent upon dapagliflozin AUC, the effect of food on dapagliflozin  $C_{max}$  is unlikely to have a clinically meaningful effect on dapagliflozin's efficacy. Thus the effect of food on dapagliflozin  $C_{max}$  is not considered clinically meaningful. A light-fat meal did not appear to have an effect on  $C_{max}$ ,  $AUC_{(0-T)}$ , and  $AUC_{(INF)}$  of metformin in either strength of the dapagliflozin/metformin XR FDC formulations compared to the fasted state.

Additional supporting bioequivalence data suggest consistent and comparable performance of 5/500 and 10/1,000 mg dapagliflozin/metformin XR FDC at steady state (Studies MB102025, MB102092 and MB102100).

Overall, bioequivalence of the 5/500 mg and 10/1,000 mg dapagliflozin/metformin XR FDC tablets relative to the individual components co-administered in fed healthy subjects was demonstrated. The request for a waiver from conducting studies with the 5/1,000 and 10/500 mg tablets is acceptable.

## Pharmacodynamics

### Studies providing pharmacodynamic data

The sponsor considers that the clinical pharmacology programme that supported the initial dapagliflozin dossier also provides relevant information to support the dapagliflozin/metformin XR FDC programme. No additional specific clinical pharmacology studies were conducted for this submission.

**Dosage selection for the pivotal studies**

The approved dose of dapagliflozin is 10 mg. In the original application the 5 mg dose was not approved due to lack of data to support its use.

The approved starting dose for metformin XR is 500–750 mg once daily given with the evening meal. The dose may be increased to maximum recommended dose of 2000 mg per day.

The justification of the inclusion of the 5 mg/1000 mg dapagliflozin/metformin XR FDC is to allow for the administration of 2 x 5/100 mg tablets to achieve the equivalent of the maximum daily recommended dose of dapagliflozin/metformin XR 10 mg/2000 mg.

**Efficacy****Studies providing efficacy data**

No clinical studies have been conducted using the FDC tablets. Efficacy is based on the studies which were conducted using co-administration of the two individual components of the FDC.

Eight clinical efficacy studies were submitted in support of this application. All had been previously evaluated in the original application to register dapagliflozin (PM-2010-03812-5) and the application for extension of indication and changes to the dapagliflozin PI (PM-2013-01503-1-5).

New data for one study was submitted in this application, comprising new long term data for Study D1690C00012<sup>7</sup>.

Study D1690C00012A is a 24 week, multicentre, international, double blind, randomised, parallel group, placebo controlled, Phase III study with a 78 week extension period to evaluate the effect of dapagliflozin in combination with metformin on body weight in subjects with T2DM who have inadequate glycaemic control on metformin alone. The primary objective is to assess the same objectives as for the 24 week short term treatment period after 102 weeks of double blind treatment.

Patients were administered dapagliflozin 10 mg or matching placebo as add-on therapy to metformin during the short term (24 weeks) and long term (78 weeks) periods:

- Change in total body weight from baseline to week 102
- Change in waist circumference from baseline to week 102
- Change in total body fat mass from baseline to week 102
- Proportion of subjects with body weight decrease  $\geq 5\%$  from baseline to week 102.

Details of other (previously evaluated) efficacy studies submitted in support of this application are provided in Attachment 2, Extract from the clinical evaluation report.

**Evaluator's conclusions on efficacy**

- No studies were conducted using the FDC tablets. The efficacy data is based on the extrapolation of data from studies using co-administration of the individual components.

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<sup>7</sup> Short term data from this study were evaluated for the original submission to register dapagliflozin.

- A 2-way drug interaction study was submitted in the original application and was accepted as showing no clinically meaningful effect of dapagliflozin on metformin PK, and vice versa.
- All the studies submitted in this application have been previously submitted in the original submission and the submission for extension of indication (add on to dipeptidyl peptidase-4 (DPP-4) inhibitor). The long term extension studies confirm the short term treatment period and do not add any new safety concerns. The co-administration of dapagliflozin and metformin has been accepted as efficacious with the benefits outweighing the risks.
- The studies submitted are consistent and demonstrate that dapagliflozin in initial combination with metformin achieves a significantly greater reduction in HbA1c than is achieved by metformin alone. The quantum of difference in HbA1c of 0.54-0.70 seen in Studies MB102021 and MB10234 are clinically significant. In these studies the approximately 2-3 kg greater weight loss was also achieved with the combination therapy. While this is a modest decrease in weight it is significant in that other therapy options were weight neutral or lead to increased weight, a significant issue in the management of T2DM. The change in HbA1c is generally evident after one week's treatment in many of the studies, irrespective of the background therapeutic combination.
- The only question is whether the studies of the co-administration of the two components are acceptable as a surrogate for studies in which the FDC was used.
- Given the bioequivalence of the FDC tablets with the individual components there seems no reason to believe that the FDC will not be as effective and the safety profile the same as the co-administration of the individual components.
- In the original application the 5 mg tablet was not approved based on the evidence that it was not as effective as the 10 mg tablet and that there was a risk of its use in patients who were at greater risk of side effects such as mild renal dysfunction. No further justification is provided in this application for the 5 mg strength and the only argument given is that it is an alternate method of providing for patients requiring 10 mg dapagliflozin and 2,000 mg metformin (by taking 2 tablets of 5 mg dapagliflozin/1,000 mg metformin). This is not sufficient reason for the approval of the 5 mg tablet. The same dose can be achieved by taking 1 tablet of 10 mg dapagliflozin and 2 tablets of 1,000 mg metformin XR.
- It is recommended that FDC tablet be taken in the evening, in line with the recommendation that the metformin XR tablet be taken in the evening. Study MB102013 demonstrated that the evening dosing of dapagliflozin provided similar efficacy to the morning dosing.

## Safety

### Evaluator's comment:

Given that there were no studies using the FDC tablets the safety data is all based on the co-administration of the individual components. Further no pooling of studies was performed by the sponsor "because of the inherent limitations associated with interpretation of data combined from studies with differing study designs and treatment durations."

The Summary of Clinical Safety simply presents the results for each individual study without dissecting out the combination of dapagliflozin + metformin in relation to the other combinations or therapy given. No pooled data is provided. The focus of the

summaries is on dapagliflozin rather than the combination and the results are presented as dapagliflozin versus comparators rather than dapagliflozin + metformin versus comparators. This has been corrected where possible.

All the efficacy studies have been evaluated previously in other applications and the safety found to be acceptable. The additional long term safety data new to this application has not raised any new safety issues.

In the absence of studies using the FDC, the relevant adverse events (AE) profile is to compare dapagliflozin + metformin with dapagliflozin alone and metformin alone or with other combinations of OADs. Only Study MB102034 compared the combination of 10 mg dapagliflozin + metformin to the individual components alone over 24 weeks. This study is presented as the pivotal study. Study MB102021 has also been included as a pivotal study (for safety) as it compared 5 mg dapagliflozin + metformin versus dapagliflozin and metformin alone.

Studies in which the co-administration of 10 mg dapagliflozin + metformin can be compared to other combinations of OADs are presented as 'other' studies. This is not how the applicant has presented the data but allows for a more appropriate review of the safety data. Study MB10213 is excluded as it included only dapagliflozin monotherapy.

### Studies providing safety data

The following studies provided evaluable safety data:

#### *Pivotal efficacy studies*

In the pivotal efficacy studies, the following safety data were collected:

- General AEs were assessed by collecting all AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation at study visits
- AEs of particular interest, including hypoglycaemic events, urinary tract infections (UTIs), genital infections, renal safety, malignancies and other tumours, hepatic safety, cardiovascular safety, and bone metabolism, were assessed by questioning the patient about all symptoms reported in the diary and for determining if they met the clinical definition of hypoglycaemia.
- Laboratory tests, including standard haematology, clinical chemistry and urinalysis, were performed at screening, baseline, and at each study visit up to 51 weeks. ECG was performed at baseline and at Weeks 24 and 48, and vital signs and physical examination were evaluated at each study visit.

### Patient exposure

Table 3 shows exposure to dapagliflozin and comparators in clinical pharmacology studies

**Table 3: Exposure to dapagliflozin and comparators in clinical pharmacology studies**

Study	Number enrolled	Dapa/met XR FDC	Dapa + Met components	Met XR alone Glucophage
MB102060	15	0	0	15
MB102065	15	15	15	0

Study	Number enrolled	Dapa/met XR FDC	Dapa + Met components	Met XR alone Glucophage
MB10271	15	15	15	0
MB102092	36	36	36	0
MB102100	36	36	36	0
MB102125	72	72	72	0
CV181120*	28	0	0	28#
TOTAL	217	174	174	28

\* Study CV 181120 was not included in the Summary of Clinical Safety. # Subjects also received Diabex XR

In the 8 efficacy studies included in the submission:

- 4594 patients were randomised;
- 1668 received dapagliflozin + metformin (some in combination with sitagliptin or insulin);
- 1383 receive dapagliflozin (alone or plus sitagliptin alone or in combination with insulin with or without other OADs (other than metformin alone));
- 1543 received control/comparator.

Exposure to dapagliflozin, with or without metformin and/or other OADs in clinical efficacy studies is shown in Table 4 and Table 5.

**Table 4: Exposure to dapagliflozin, with or without metformin and/or other OADs in clinical efficacy studies**

Studies	N	Placebo /control	Dapa + Met	Dapa alone	Dapa + OADa
MB102014	546	137	409	0	0
D1690C00012	182	91	91	0	0
D1690C00004	814	408	406	0	0
MB102034	638	208b	211	219	0
MB102021	598	201b	194	203	0
D1690C00010 (Stratum 1)	223	112	0	0	111
D1690C00010 (Stratum 2)	228	114	114	0	0
D1690C00006	807	197	243c	304d	63

Studies	N	Placebo /control	Dapa + Met	Dapa alone	Dapa + OADa
MB102013 (Group 1)	485	75	0	410	0
MB102013 (Group 2)	73	0	0	73	0
Total	4594	1543	1668	1209	174

Dapa = dapagliflozin; Met = metformin; N number of non-missing observations; OAD oral anti-diabetic drug.

a Numbers reported based on enrolled subjects who took Dapa + open label insulin + OADs other than Met alone (D1690C00006) and Dapa + sitagliptin alone (D1690C00010). b For studies MB102034 and MB102021, dapagliflozin monotherapy plus metformin XR monotherapy were used as control. c For study D1690C00006, numbers reported based on enrolled subjects in Strata 2 who took insulin plus metformin alone only. d For study D1690C00006, numbers reported based on enrolled subjects in Strata 1 who took insulin with no OADs

**Table 5: Duration of exposure to dapagliflozin plus metformin combination**

Study	N	Mean duration; days		Median duration; days		Cumulative exposure (patient years)	
		Dapa* + met	Placebo or comp	Dapa + met	Placebo or comp	Dapa+ met	Placebo or comp
MB_014	546	599.3	541.1	712.0	701.0	221.5	203.0
D16_012	182	612.1	642.1	714.0	714.0	152.5	160.0
D169_004	814	539.1	560.6	721.0	709.5	623.2	602.2
MB_2034	638	154.2	155.9	168	168	NP	NP
MB_2021	598	159.3	153.2, 154.6	168	168	NP	NP
D16_0010 (Stratum 1)	223	308.1	306.9	337.0	337.0	93.6	94.1
D16_0010 (Stratum 2)	228	321.3	304.6	337.0	337.0	100.3	95.1
D169_006	807	596.6	516.5	727	721	321.0	278.6
MB_2013	485	543.1	515.9	700.0	707.0	99.6	105.9
<b>Total</b>	<b>4594</b>						

\* dapa (dapagliflozin) 10 mg strength reported when range of doses tested; met = metformin; comp = comparator. N = number of subjects

The dose of metformin in the efficacy studies varied with the majority of patients received metformin at a dose of 1,500 to 2,500 mg per day (3,000 mg was the maximum in Study MB102014). The medium exposure to metformin XR was 2,000 mg in all treatment groups.

## Safety issues with the potential for major regulatory impact

### **Renal impairment**

Renal impairment or failure is identified as a potential risk in the Risk Management Plan (RMP) because the target organ of dapagliflozin is the kidney. In the efficacy studies, a slight increase in AEs related to renal impairment or failure was reported for dapagliflozin versus comparator for patients  $\geq 65$  years of age and for subjects with moderate renal impairment, but not for the population as a whole. Dapagliflozin is not associated with a deleterious effect on renal function. Serious AEs (SAEs) of renal impairment are rare and balanced across treatment groups. The renal effects seen with dapagliflozin are generally of minor clinical importance and appear to be attributed to reversible haemodynamic changes rather than direct renal toxic effects. The changes are generally modest, transient and reversible changes in laboratory tests, such as serum creatinine or estimated glomerular filtration rate (eGFR). A review of the total AE database found that the proportion of subjects whose creatinine values returned to baseline following discontinuation of treatment (defined as baseline plus 20%) was similar between those taking dapagliflozin (86/106, 81.1%) and placebo/comparator (46/61, 75.4%).

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (Forxiga PI). Dapagliflozin is not recommended for use in patients with severe renal impairment (creatinine clearance (CrCl)  $< 60$  mL/min or eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>).

Metformin is contraindicated in patients with moderate to severe renal impairment (CrCl  $< 60$  mL/min). The Diabex XR PI also advises caution as age increases because metformin is eliminated by the kidney, and elderly patients are more likely to have decreased renal function. Monitoring of renal function is necessary to prevent metformin associated lactic acidosis, particularly in the elderly.

### **Liver toxicity**

Liver injury is included as a potential risk in the RMP due to one subject in Study D1690C00004<sup>8</sup> experiencing an AE with the diagnosis of drug induced hepatitis and/or autoimmune hepatitis. Hepatic function was monitored in all the clinical studies with special attention to increased liver function tests (as required in FDA Guidance document: *Drug Induced Liver Injury (DILI): Premarketing clinical Evaluation*, FDA, 2009). A review of all AEs reported in the clinical studies found that there was no clear association between dapagliflozin and liver toxicity. In this analysis, the combination of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 3$  x upper limit of normal (ULN) with concomitant or subsequent total bilirubin (TBL)  $\geq 2$  x ULN was reported in  $\leq 0.2\%$  of patients treated with dapagliflozin or control. All of these patients had co-morbidities that could explain these events.

The dapagliflozin/metformin XR FDC is contraindicated in patients with hepatic impairment, in line with the metformin prescribing information, because of the risk of lactic acidosis associated with metformin in patients with impaired hepatic function.

### **Cardiovascular safety**

No new safety signal regarding cardiovascular related AE was observed with dapagliflozin as add-on to metformin or in the long term extension of the efficacy studies submitted in this submission.

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<sup>8</sup> Identified in original submission to register dapagliflozin and included in the Forxiga PI

**Other safety issues*****Safety in special populations***

No studies were conducted using the dapagliflozin/metformin XR FDC.

***Safety related to drug-drug interactions and other interactions***

A 2-way PK drug interaction study between dapagliflozin and metformin was performed in healthy volunteers (Study MB102026 included in the initial dapagliflozin dossier). The subjects received single doses of 20 mg of dapagliflozin and 1,000 mg of metformin either individually or concurrently. There was no effect of either metformin on the PK of dapagliflozin or dapagliflozin on the PK of metformin.

No interaction studies have been performed for the dapagliflozin/metformin XR FDC.

Recommendations related to drug interactions are based on the existing recommendations in the individual component PIs.

**Evaluator's conclusions on safety**

- Based on the studies submitted, it appears that the safety profile of the combination of dapagliflozin and metformin is similar to that of dapagliflozin and metformin alone. The issues raised in the evaluation of the dapagliflozin original submission, namely an increase in genital and urinary tract infections, and increase in haematocrit, remain with the combination. No new safety signals emerged in the study of dapagliflozin add on to metformin in combination with a DPP-4 inhibitor or in the long term administration (up to 2 years) of dapagliflozin add on to metformin therapy, when compared to a sulphonylurea, or in combination with insulin with or without other OAD.
- The frequency of hypoglycaemia for the dapagliflozin + metformin combination was low and not increased with the combination compared to dapagliflozin alone.
- The initial concerns over an increased incidence of breast, prostate and bladder cancer does not appear to be confirmed with the long term extensions of the studies.
- The known safety profiles of dapagliflozin and metformin are reflected in the proposed PI for the combination product.

**First round benefit-risk assessment****First round assessment of benefits**

The benefits of dapagliflozin/metformin XR FDC in the proposed usage are:

- Use of a combination product allows a reduction in the number of tablets taken by patients prescribed multiple OADs.
- The combination of dapagliflozin plus metformin provides an effective and convenient treatment option for patients who have inadequate glycaemic control on metformin alone, or metformin in combination with other antidiabetic drugs including DPP-4 inhibitors and insulin.
- Dapagliflozin 10 mg add on to metformin was demonstrated to consistently reduce HbA1c in various clinical settings. The HbA1c lowering effect persisted up to 104 weeks, together with modest but sustained weight loss during the extended period.
- Dapagliflozin 10 mg add on to metformin was non inferior to glipizide plus metformin in terms of HbA1c lowering. Further events of confirmed hypoglycaemia were 10



times higher with glipizide than with dapagliflozin plus metformin and weight gain was observed with glipizide while dapagliflozin led to a modest but sustained weight loss.

- Dapagliflozin plus metformin has a low propensity for hypoglycaemia.
- No new safety signals were identified for the combination of dapagliflozin plus metformin.

### First round assessment of risks

The risks of dapagliflozin/metformin XR FDC in the proposed usage are:

- The risk of increased genital and urinary tract infections identified with dapagliflozin monotherapy remain with the combination of dapagliflozin and metformin.
- Potential risks of hypoglycaemia, volume depletion, increased haematocrit, renal impairment, bone fracture, liver injury and bladder, prostate and breast cancer, as described with dapagliflozin monotherapy, remain with the combination of dapagliflozin and metformin.
- The risks of metformin monotherapy, namely lactic acidosis, remain with the combination of dapagliflozin and metformin.

### First round assessment of benefit-risk balance

The benefit-risk balance is not favourable for the dapagliflozin 5 mg combination, that is, dapagliflozin/metformin 5/1,000 mg.

The benefit-risk balance for other strengths awaits revisions to the PI.

### First round recommendation regarding authorisation

The 5 mg/1,000 mg strength should be rejected on the basis that no additional data was submitted addressing the issues relating to the reasons for its rejection in the initial application; that is, insufficient efficacy for the 5 mg strength of dapagliflozin. Given the concerns raised about this strength, it is not accepted that it is necessary for the achievement of appropriate dosing in all patients.

Recommendations for other strengths await revisions to the PI (see below).

### Clinical questions

The proposed PI consists of a combination of the Forxiga and Diabex PIs with updated *Clinical Trial* section based on the submission of the extension of indication to include add on to a DPP-4 inhibitor (Study D1690C00010) and the additional long term data for Studies D1690C00004 and D1690C00006.

1. The proposed indication: "*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.*" is non-specific. A more specific indication, reflecting the mono product indications, should be substituted.
2. The PI needs to be amended to include the recommendations of the outcome of the evaluation for the extension of indication and additional long term data.
3. All reference to the 5 mg/1,000 mg combination tablet should be removed.
4. The adverse reactions section presents AEs for dapagliflozin versus placebo for 24 weeks. The total for "dapagliflozin" included 4 monotherapy and 6 initial or add on

studies with metformin. It is not appropriate to include the monotherapy studies in this table for the FDC. The table should be amended to the data from at least study MB102034 which compared the combination to the individual components which gives a truer indication of the likely effect of the FDC tablet over the individual components.

5. The black box warning appears in the section relating to *Dosage and Administration* which is not consistent with the Diabex XR PI where the box warning is at the start of the PI

Please provide a revised PI taking into consideration the revisions requested for the previous dapagliflozin PI (submission 2013-01503-1-5) and the comments above.

Should you wish to retain the 5/1000 mg tablet; further justification should be provided.

## Second round evaluation of clinical data submitted in response to questions

### Question 1:

The proposed indication: "*XIGDUO XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.*" is nonspecific. A more specific indication, reflecting the mono product indications, should be substituted.

### **Sponsor's response:**

The sponsor considers the proposed indication is appropriate for use of the FDC in a manner consistent with the approved usage of the mono-components. The proposed indication applies to the situation where the FDC is used in place for the separately administered products when the two mono-components are taken together, either as add-on or initial combination therapy, as justified by clinical evidence; as well as the instance, where substituting the use of the FDC in the situation where the specific patient is already receiving the two drugs is appropriate. The sponsor considers the evidence submitted with this application support efficacy and safety in either of these situations, and it is therefore felt that the phrasing of the indication as "when treatment with both dapagliflozin and metformin is appropriate" is acceptable. Additionally the sponsor considers that the information in the remainder of the PI (*Clinical trials, Precautions, Dosage and Administration* and other sections) allows for the safe and efficacious use of the FDC.

### **TGA evaluation of response:**

The EMA indication for Xigduo (dapagliflozin 5 mg/metformin 850 mg) is:

*Xigduo is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:*

- *In patients inadequately controlled on their maximally tolerated dose of metformin alone*
- *In combination with other glucose-lowering medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products (see sections 4.4, 4.5 and 5.1 for available data on different combinations)*
- *In patients already being treated with the combination of dapagliflozin and metformin as separate tablets.*

Along these lines, the TGA indication should read something like:

*Xigduo XR is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:*

- *In patients inadequately controlled on their maximally tolerated dose of metformin alone*
- *In combination with other glucose-lowering medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products (see sections CLINICAL TRIALS)*
- *In patients already being treated with the combination of dapagliflozin and metformin as separate tablets.*

**Question 2:**

*The PI needs to be amended to include the recommendations of the outcome of the evaluation for the extension of indication and additional long-term data.*

**Sponsor response:**

The Xigduo XR PI has been updated to be consistent with the recommendations made as part of the Forxiga evaluation for the extension of indication and additional long-term data that is currently under review (Submission ID: PM-2013-01503-1-5).

**TGA evaluation of sponsor response:**

The response is acceptable.

**Question 3**

*All reference to the 5 mg/1,000 mg combination tablet should be removed*

**Sponsor response:**

The sponsor notes that the clinical evaluation report includes the following text in relation to the acceptability of the 5 mg/1,000 mg strength.

*“The 5 mg/1,000 mg strength should be rejected on the basis that no additional data was submitted addressing the issues relating to the reasons for its rejection in the initial application; that is, insufficient efficacy for the 5 mg strength of dapagliflozin. Given the concerns raised about this strength, it is not accepted that it is necessary for the achievement of appropriate dosing in all patients.”*

The sponsor wishes to clarify there is no intention or proposal within the current submission to obtain approval for use of dapagliflozin at a dose of 5 mg. The proposed dose of dapagliflozin as part of this application is consistent with the dose approved in the initial application (that is, 10 mg). There are a significant number of patients that require increases in metformin to 2,000 mg to assist in management of their condition and the 5 mg/1,000 mg tablet has been developed to allow the delivery of this maximum metformin dose. Due to physical limitations of the formulation a single tablet containing 10 mg dapagliflozin and 2,000 mg metformin would be of such dimensions that it would prove difficult for most patients to swallow and as a result patient acceptability would be severely compromised.

Consequently, when taken as two tablets taken together once daily (as described in the *Dosage and Administration* section of the PI), the 5 mg/1,000 mg dose form provides 10 mg dapagliflozin (consistent with the approved dose of the mono-component) and the maximum metformin dose (2,000 mg). The sponsor considers the 5 mg/1,000 mg tablet essential to avoid potential confusion that could arise should a patient be instructed to combine a 10 mg/1,000 mg FDC with a free form extended release metformin tablet to achieve a 2,000 mg metformin dose. Additionally, when administered in this manner, the FDC provides for a reduction in the overall number of tablets compared to administration of the free form of the medicines separately, resulting in ease of administration for

patients and less chance for dosing errors. Given the physical limitations of the dose form, the need for an available 2,000 mg metformin dose and reduction in pill burden for patients, the sponsor considers the 5 mg /1,000 mg presentation to be appropriate when used in accordance with the dosing recommendation in the proposed PI.

***TGA evaluation of sponsor's response***

A 2000 mg dose of metformin could be obtained by combining the 10 mg/1000 mg tablet with a 1000 mg tablet of metformin. The *Dosage and Administration* section would need to be edited to reflect this.

**Question 4**

*The adverse reaction section presents AEs for dapagliflozin versus placebo for 24 weeks. The total for "dapagliflozin" included 4 monotherapy and 6 initial or add on studies with metformin. It is not appropriate to include the monotherapy studies in this table for the FDC. The table should be amended to the data from at least study MB102034 which compared the combination to the individual components which gives a truer indication of the likely effect of the FDC tablet over the individual components.*

***Sponsor response:***

The current *Adverse Effects* section provides a view of the safety of dapagliflozin and metformin, which is consistent with the experience gained with the mono-components. The presentation of results drawn exclusively from trials studying combined use of dapagliflozin and metformin may provide a perspective of AEs to be expected with the FDC however the use of the components together does not preclude the occurrence of an AE that may be experienced with either component as monotherapy. Overall, the safety profile of dapagliflozin in combination with metformin is consistent with the safety profiles of the individual components. Furthermore no additional adverse reactions were identified in a pooled analysis of dapagliflozin plus metformin studies compared with those reported for the individual components. The pooled data for dapagliflozin versus placebo including the monotherapy studies draws on increased exposure of dapagliflozin and will more reliably inform prescribers regarding potential AEs that may be experienced by patients using the FDC. Therefore, the sponsor considers amendment of the table as requested has the potential to reduce the reliability and extent of the safety information available to the prescriber and has retained the table including pooled monotherapy results.

***TGA evaluation of sponsor's response:***

The response is acceptable.

**Question 5**

*The black box warning appears in the section relating to Dosage and Administration which is not consistent with the Diabex XR PI where the box warning is at the start of the PI.*

***Sponsor response:***

During a review of available approved PIs for other products containing metformin, the sponsor has noted that the black box warning specific to lactic acidosis is either placed at the beginning of the PI or at the start of the *Dosage and Administration* section. As either location appears to be considered acceptable by the TGA for the purposes of being a prominent location in PI, the sponsor proposes to retain the black box warning in its present location in the *Dosage and Administration* section. This approach is consistent with other recently approved metformin containing FDC products.

**TGA evaluation of sponsor response:**

The response is acceptable.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan, EU Risk Management Plan Version 2 Dated 17<sup>th</sup> June 2013 (data lock point 1<sup>st</sup> May 2012), with Australian Specific Annex Version 2 Dated 6<sup>th</sup> August 2013, which was reviewed by the TGA's Office of Product Review (OPR).

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

**Table 6: Summary of ongoing safety concerns**

Ongoing safety concerns	
<b>Important identified risks</b>	<ul style="list-style-type: none"> <li>· Genital Infections</li> <li>· Urinary Tract Infections</li> <li>· Lactic Acidosis</li> </ul>
<b>Important potential risks</b>	<ul style="list-style-type: none"> <li>· Hypoglycemia</li> <li>· Volume Depletion</li> <li>· Clinical Consequences of Increased Hematocrit</li> <li>· Renal Impairment/Failure</li> <li>· Bone Fracture</li> <li>· Liver Injury</li> <li>· Bladder Cancer</li> <li>· Breast Cancer</li> <li>· Prostate Cancer</li> <li>· Off-label use of dapagliflozin in specific populations</li> <li>· Pelvic dilatation (renal) in rat pre- and post-natal development, juvenile toxicity studies</li> <li>· Glucosuria and reduced weight among rat pups in pre- and post-natal development toxicity studies</li> </ul>
<b>Important missing information</b>	<ul style="list-style-type: none"> <li>· Pediatric Population</li> <li>· Pregnancy and Lactation</li> </ul>

Ongoing safety concerns	
	<ul style="list-style-type: none"> <li>· Elderly (&gt; 75 years)</li> <li>· Severe renal impairment</li> <li>· Moderate and severe hepatic impairment</li> <li>· Congestive heart failure defined as New York Heart Association (NYHA) class III and IV</li> </ul>

### Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities. There are no specific studies proposed for the dapagliflozin and metformin FDC. According to the sponsor, patients treated with dapagliflozin and metformin FDC will be included in the pharmacoepidemiology program described in the dapagliflozin RMP, which includes studies of the following:

- Severe complications of UTI
- Risk of acute hepatic failure
- Risk of acute renal failure
- Risk of cancer
- Cardiovascular risk
- Bladder cancer
- Liver injury
- Off-label use
- Elderly population
- Elderly population; CHF NYHA Class III and IV.

The sponsor also proposes to study the following using targeted questionnaires as part of the pharmacovigilance plan:

- Genital infection
- Urinary tract infection
- Renal impairment/failure
- Liver injury
- Bladder Cancer
- Breast cancer
- Prostate cancer.

### Risk minimisation activities

The sponsor proposes only routine risk minimisation activities and makes the following comment regarding additional risk minimisation activities in the RMP: *“For the potential safety concerns, the product labelling ([PI and Consumer Medicine Information (CMI)]) is adequate to communicate risk. No additional risk minimization measures are planned for each important identified or potential risk. Supporting data throughout this RMP based on*

*the dapagliflozin Phase 3 program and published data on metformin are sufficient to assess potential risks in the context of the approved indications.”*

### Reconciliation of issues outlined in the RMP report

Table 7 summarises the OPR’s first round evaluation of the RMP, the sponsor’s responses to issues raised by the OPR and the OPR’s evaluation of the sponsor’s responses.

**Table 7: Reconciliation of issues outlined in the RMP report**

Recommendation in RMP evaluation report	Sponsor’s response	OPR evaluator’s comment
<p>Please provide further information on the death of the patient taking dapagliflozin as reported in the PSUR 1(2010-03812-3-5).</p>	<p>This patient with a remarkable history of coronary artery disease experienced stenocardia while on treatment with dapagliflozin. The dechallenge appears to be positive. Causality relationship is assessed as possible. It was reported that the patient died probably from cardiac cause. Death, reported as an event, is considered not related to dapagliflozin and most likely due to cardiac cause. Full details of this death are provided.</p>	<p>This is acceptable.</p>
<p><i>General statements: EU RMP:</i></p> <p>The sponsor should ensure that all changes, additions and deletions are tracked.</p> <p>The sponsor should improve the consistency of the version numbers and labelling.</p> <p>Many sections within the EU-RMP are out of date [and require updating].</p>	<p>An updated EU RMP Version 3 is provided as part of this response. This is the first EU RMP in AUS format so will be numbered version 1.</p> <p>Another change between EU RMP Versions 2 and 3 to be noted is, the important potential risks of “Pelvic dilatation (renal) in rat pre- and post-natal development juvenile toxicity studies” and “Glucosuria and reduced weight among rat pups in pre- and post-natal development toxicity studies” included in Version 2 of the EU RMP in error due to a misunderstanding by the sponsor of the European regulatory requirements have been removed in Version 3 of the EU RMP.</p> <p>The updated EU RMP version 3 (EU RMP in AUS format version 1) has the same data</p>	<p>The evaluator notes the sponsor’s commitment to update the RMP as requested and this is acceptable.</p>



Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	lock date (01 May 2012) as EU RMP version 2. The EU RMP will be updated with the next data lock update.	
<p><i>General Statements: ASA</i></p> <p>It is recommended that the ASA be amended to include the following:</p> <p>a. A table outlining the ASA version numbers and any updates/changes.</p> <p>b. It is noted that ASA Versions 1-4 appear to be exactly the same in content.</p> <p>c. Australian specific epidemiological information.</p> <p>d. All ongoing and planned studies in the pharmacovigilance plan, including milestones and expected submission of study reports to Australia.</p> <p>e. All routine risk minimisation activities for each ongoing safety concern, including a table showing the wording used in the corresponding section of the proposed Australian PI.</p>	<p>a. An updated ASA Version 3 is being provided as part of this response.</p> <p>The main difference from version 1 to 2 has been updates made to the ASA Versions 1 to 2 to reflect changes in document version numbers, with no change to the pharmacovigilance or risk minimisation activities proposed. Details are provided for the updates between versions and all changes between ASA Version 2 and 3.</p> <p>b. The sponsor acknowledges the RMP evaluator's comment that dapagliflozin/metformin ASA Versions 1-2 appear to be exactly the same in content. The sponsor confirms that this is correct, there have been no additional risks, pharmacovigilance or risk minimisation activities proposed from Version 1 to 2.</p> <p>c. Australian specific epidemiological information is now included in the updated ASA (version 3).</p> <p>d. EU RMP Version 3, table 3.5.1-1 summarises the ongoing and planned additional pharmacovigilance studies and activities in the Pharmacovigilance Plan for dapagliflozin/metformin, including the objectives, safety concerns, status, and date of the interim or final reports. Please note that the ASA only includes activities specific to Australia which are not included in the EU RMP. As a consequence, the updated ASA does not include this information as it is included in</p>	<p>This is acceptable.</p>



Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p>the EU RMP.</p> <p>e. The ASA Version 3 includes a table showing the proposed Australian PI text for identified and potential risks.</p>	
<p><i>Ongoing Safety Concerns:</i></p> <p>It is recommended that the following risks should be added to the list of ongoing safety concerns:</p> <p>a. Malignancy (Important missing information)</p> <p>b. Off-label use in obese patients who do not have type 2 diabetes mellitus (T2DM)</p> <p>c. Urosepsis</p> <p>d. Concomitant use with other glucagon like peptides 1 (GLP-1) analogues (Important missing information)</p> <p>e. Patients with body mass index (BMI) &gt; 45 (Important missing information)</p>	<p>In addition to the action plan outlined for dapagliflozin in the dapagliflozin RMP, no further activities are planned for the dapagliflozin and metformin FDC based on the well-known safety profile of metformin. Patients exposed to dapagliflozin and metformin FDC are included in the pharmacoepidemiology program proposed in the dapagliflozin EU RMP.</p> <p>The TGA's evaluation of the dapagliflozin clinical program and associated RMP in the original registration submission for Forxiga (PM-2010-03813-3-5) did not request the 'ongoing safety concerns' a-e. Data in the current submission does not indicate any changed safety signal with respect to any of the requests a-e relative to the original submission.</p> <p>The sponsor has also provided individual justifications against adding each safety concern [not included here].</p>	<p>The RMP evaluation report recommended that the following risks should be included in the list of ongoing safety concerns as important missing information: Malignancy, Off-label use in obese patients who do not have type 2 diabetes mellitus (T2DM), Urosepsis, Patients with BMI &gt; 45. This is consistent with recommendations made in a recent RMP evaluation (and subsequent round 2 RMP advice) for the single ingredient dapagliflozin product Forxiga (PM-2013-01503-1-5).</p> <p>These recommendations are maintained.</p>
<p><i>Ongoing Safety Concerns</i></p> <p>It is noted that occasionally patients may experience passing of a soft, hydrated mass in the faeces. The sponsor is requested to clarify if there have been any reports of bowel obstruction or PR bleeding in patients taking this FDC of dapagliflozin and metformin.</p>	<p>The sponsor has provided clarification.</p>	<p>This is acceptable.</p>
<p><i>Pharmacovigilance Plan</i></p> <p>[Several] issues regarding the pharmacovigilance plan</p>	<p>Information has been provided.</p>	<p>The sponsor's response is considered acceptable. As part of the pharmacovigilance plan, revised protocols should</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
require clarification.		be provided to the TGA when available.
<p>The targeted questionnaires require updating to cater for the FDC. The questionnaires currently only apply to dapagliflozin as a monotherapy.</p>	<p>An assurance is provided that the targeted questionnaires will be updated to include the FDC in the next RMP version. Seven targeted questionnaires are being utilised as planned pharmacovigilance activities for identified risks of Genital Infections and Urinary Tract Infections, and for potential risks of Renal Impairment, Liver Injury, Bladder Cancer, Breast Cancer and Prostate Cancer.</p>	<p>For completeness, the updated questionnaires should be included as an attachment to the RMP or the ASA when they are updated. This has been recommended in previous evaluations for the single ingredient product.</p>
<p><i>Risk Minimisation</i></p> <p>Additional risk minimisation is required. The sponsor has previously agreed to additional risk minimisation activities for dapagliflozin (Forxiga). The sponsor has produced a prescriber guide, patient guide, educational materials and an Royal Australian College of General Practitioners (RACGP) accredited Active Learning Module (ALM) slide deck. The sponsor should re-submit an updated RMP in line with the updates to the dapagliflozin RMP.</p>	<p>The specific condition of registration for Forxiga was to develop an education program that provides a focus on appropriate use, including patient selection and safety issues.</p> <p>The Forxiga ASA included commitment to deliver this by 3 modes.</p> <p>This education program was [previously] approved by the OPR. Thus TGA's requirement of educating HCP's on safety profile and appropriate prescribing of dapagliflozin has been addressed. Prescribers have thus already been educated on the use of Forxiga and that includes dapagliflozin as add-on to metformin and initial combination with metformin. This is exactly how Xigduo XR will be used.</p> <p>The sponsor believes that specific information on dapagliflozin safety and appropriate use, particularly in combination with metformin, has been provided to prescribers in the Forxiga education program and that an extensive Xigduo XR specific education program</p>	<p>The evaluator has considered the sponsor's argument that delivery of the education program for the single ingredient (dapagliflozin) product negates the need for further education for the FDC product.</p> <p>The evaluator accepts that the dapagliflozin program provided health professionals with necessary information regarding the appropriate use of dapagliflozin.</p> <p>The evaluator also accepts that metformin is a well known product in the Australian market.</p> <p>Therefore the sponsor's justification for requiring no additional education program for the FDC, from a RMP standpoint, is accepted.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p>will not provide any significant or additional information on dapagliflozin regarding the use of the combination.</p> <p>The RMP developed for dapagliflozin/metformin FDC has been on the principle that all the action plans are outlined for dapagliflozin in the dapagliflozin RMP, and no further activities are planned for the dapagliflozin and metformin FDC based on the well-known safety profile of metformin.</p> <p>Given the above no further risk minimisation activities for dapagliflozin/metformin FDC are required.</p>	
<p><i>Risk Minimisation</i></p> <p>The sponsor has not adequately addressed the risk of medication error within the EU-RMP or the ASA. The above statement only addresses dapagliflozin and should be updated to consider the current application.</p>	<p>The section on medication errors in the RMP has been updated with descriptions of mitigation actions taken to prevent medication errors. The Xigduo XR CMI has also been amended to include a statement reminding patients that they should not take other metformin or dapagliflozin tablets whilst taking the combination tablet.</p>	<p>This is acceptable.</p>
<p><i>PI and CMI</i></p> <p>In the RMP evaluation report the evaluator has recommended several revisions to the draft PI document for consideration by the Delegate.</p> <p>Details of these are beyond the scope of the AusPAR.</p>	<p>[Details are beyond the scope of the AusPAR].</p>	<p>PI recommendations made to the Delegate are maintained by the evaluator.</p>

### Summary and recommendations

It is considered that the sponsor's response to the OPR recommendations and requests for information has adequately addressed all of the issues identified in the RMP evaluation report with the exception of those identified in the Table above (see also *Outstanding issues* below)

### **Outstanding issues**

- Issues in relation to the RMP

An updated version of the RMP was provided with the sponsor's response to TGA request for information. This update, as well as assurances provided by the sponsor, has satisfactorily addressed many of the issues in the RMP evaluation report.

The RMP evaluation report recommended that the following risks should be included in the list of ongoing safety concerns as important missing information: Malignancy, Off-label use in obese patients who do not have T2DM, Urosepsis and Patients with BMI > 45. This is consistent with recommendations made in a recent RMP evaluation of the single ingredient dapagliflozin product Forxiga (PM-2013-01503-1-5). These recommendations are maintained.

In regards to routine risk minimisation, the recommended changes to the draft PI made in the RMP evaluation report are deferred to the Delegate.

The evaluator has accepted the sponsor's justification provided in the response to the TGA request for information that no further education is required (apart from that already delivered for the single ingredient dapagliflozin product) as additional risk minimisation.

### **Advice from the Advisory Committee on the Safety of Medicines (ACSOM)**

ACSOM advice was not sought for this submission.

### **Comments on the safety specification of the RMP**

- Clinical evaluation report

The clinical evaluator has provided the following comments in the clinical evaluation report regarding the safety specification of the RMP: *The Safety Specification in the draft RMP is satisfactory.*

- Nonclinical evaluation report

The non-clinical evaluator has provided the following comments in the non-clinical evaluation report regarding the safety specification of the RMP:

*The nonclinical Safety Specification of the draft RMP focuses solely on studies with dapagliflozin. The recommendations in the original dapagliflozin nonclinical evaluation report (PM-2010-03812-3-5) do not appear to have been incorporated. These recommendations are reproduced below and the Safety Specification should be amended accordingly or a justification provided for not doing so.*

*A higher risk of urinary tract infections may be predicted in patients with diabetes taking dapagliflozin. There is a theoretical risk of urothelial lesions associated with chronic inflammation. The urothelial hyperplasia mentioned under the heading "Renal findings in Rats" should be included in a separate heading as it is not associated with hypercalcaemia or the exacerbation of chronic progressive nephropathy. Urothelial hyperplasia was seen in the kidneys and/or bladder of some dapagliflozin treated dogs, and this lesion was attributed to urinary tract infections.*

*Delayed pubertal development was observed in treated juvenile male rats and in male pups following maternal exposure. A no observed effect level (NOEL) was not established in the juvenile study. These findings should be included in the safety specification.*

*The absence of a discussion of toxicity findings with metformin only is considered acceptable given the extensive clinical use and experience with this antihyperglycaemic agent. However, as both dapagliflozin and metformin share the kidney and adrenal glands as target organs for toxicity, this information should be included in the nonclinical Safety Specification.*

The RMP evaluator endorses the non-clinical evaluator's recommendations.

### ***Key changes to the updated RMP***

In the response to the TGA request for information the sponsor provided an updated RMP (Dapagliflozin Metformin Fixed Dose Combination EU RMP Version Number 3, Document date 16 October 2013, data lock point 1 May 2012) and Australia-specific Annex (Version Number 3, Document date 17 February 2014). Key changes from the version evaluated at Round 1 are summarised below:

**Table 8: Key changes from RMP Version 2 to Version Number 3**

RMP: Version 2 compared with Version 3	
<b>Safety specification</b>	Two safety concerns were deleted relating to a misunderstanding with the EU regulator.
<b>Pharmacovigilance activities</b>	Administrative and formatting changes were made to the annex as requested by evaluator.
<b>Risk minimisation activities</b>	Administrative and formatting changes were made to the annex as requested by evaluator.

### ***OPR evaluator's comments:***

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

### ***Recommendation***

Suggested wording for conditions of registration

- Implement Dapagliflozin Metformin Fixed Dose Combination EU RMP (Version Number 3, Document date 16 October 2013, data lock point 1 May 2012) with Australia-specific Annex (Version Number 3, Document date 17 February 2014) and any future updates as a condition of registration.

## **VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Background**

The original submission for the dapagliflozin mono product was approved by TGA on 22 October 2012. The purpose of the application is to register a new FDC product for the following indication:

*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.*

### **Quality**

The pharmaceutical chemistry evaluator recommended approval.

Because of the weight/size of the tablets, 2000 mg of metformin XR will not be marketed in a FDC tablet with dapagliflozin. The sponsor is proposing that patients requiring 2000 mg of metformin XR would take two 5 mg/1000 mg dapagliflozin/metformin XR FDC tablets.

The results of the bioequivalence studies conducted on the 10/1000 mg and the 5/500 mg tablets were noted. The pharmaceutical chemistry evaluator considered that the justification for not conducting bioequivalence studies on the 5/1000 mg tablets was acceptable from a chemistry perspective.

## Nonclinical

One repeat dose toxicity study (3 months) in rats was submitted in Module 4. The nonclinical evaluator considered that interpretation of the negative findings from the study was limited by the poor choice of doses.

However, the nonclinical evaluator concluded that registration could proceed because the mono products were already approved in free combination.

## Clinical

### Pharmacokinetics/bioequivalence studies

A 2-way drug-drug interaction study (MB102026) between dapagliflozin and metformin was submitted in the initial dapagliflozin application and found no clinically meaningful effect of dapagliflozin on metformin PK and vice versa.

Given the lack of any clinical studies specifically associated with the FDC, the approval of this FDC product relies on the bioequivalence studies.

MB102125 compared the steady-state fed bioequivalence of the proposed 10 mg/1000 mg and 5 mg/500 mg FDC tablets relative to the co-administration of the individual components of dapagliflozin and Australian-sourced Diabex XR. Participants were healthy volunteers.

**Table 9: Study MB102125, C<sub>max</sub>, AUC<sub>(0-24 h)</sub>**

	C <sub>max</sub> Geometric mean ratio (90% CI)	AUC <sub>(0-24 h)</sub> Geometric mean ratio (90% CI)
Dapagliflozin, 5 mg FDC versus mono, n = 34	0.97 (0.86, 1.09)	1.02 (0.99, 1.05)
Metformin, 500 mg FDC versus mono, n = 34	1.04 (0.99, 1.09)	1.01 (0.97, 1.05)
Dapagliflozin, 10 mg FDC versus mono, n = 35	0.99 (0.92, 1.07)	1.02 (0.99, 1.05)
Metformin, 1000 mg FDC versus mono, n = 35	1.05 (1.00, 1.10)	0.98 (0.96, 1.00)

The clinical evaluator concluded that Australian patients switching to the dapagliflozin/metformin XR FDC products from the same strengths of dapagliflozin +

Diabex XR mono products can be expected to have equivalent systemic exposures to both analytes from the FDCs. Likewise, patients taking Diabex XR who are adding dapagliflozin to their treatment regime can be expected to have equivalent systemic exposures to metformin from the dapagliflozin/metformin XR FDCs.

The results from the two supporting bioequivalence studies (MB102092 and MB102100) demonstrated bioequivalence of a 5/500 mg and 10/1000 mg dapagliflozin/metformin XR FDC tablet relative to co-administered individual component tablets (in these trials using US sourced Glucophage XR metformin) in fed healthy subjects.

The clinical evaluator advised that the waiver for the 10/500 strength was adequately justified.

### Safety

- In the clinical development program, 1668 patients received dapagliflozin and metformin (some in combination with sitagliptin or insulin).
- The longer term follow-up data, which was provided in the current dossier (compared with the initial dapagliflozin submission), has not identified any new safety concerns.
- The safety profile of metformin is well established.
- The main adverse reactions associated with dapagliflozin are:
  - Volume contraction/depletion: orthostatic hypotension, hypotension, dehydration, hypovolaemia (especially in those patients on loop diuretics and the elderly).
  - Impairment of renal function: increased serum creatinine, decreases in eGFR (especially in patients with moderate renal impairment and the elderly).
  - Genital mycotic infections
  - Urinary tract infections

There was an imbalance of bladder cancer in the clinical trials for dapagliflozin: 9 versus 1; 24.6 versus 4.3 per 10,000 patient years; relative risk (RR) = 5.4, 95% CI (0.7, 245.1). There was also an imbalance of breast cancers: 12 versus 3; RR = 2.5; 95% CI (0.6, 14.1). These imbalances appear to be the main reason for the FDA decision not to approve dapagliflozin in 2012. The FDA subsequently approved dapagliflozin in January 2014. The FDA PI warns against use in patients with bladder cancer and in patients with a history of bladder cancer. The FDA decided not to include information about the breast cancer imbalance in the PI. No imbalance for bladder or breast cancer in the clinical trial data was observed for canagliflozin (the other drug in the same class, currently registered in Australia).

### Clinical evaluator's recommendation

The clinical evaluator recommended approval, based on the bioequivalence studies.

The clinical evaluator has stated that that "... *the proposed indication is non-specific. A more specific indication, reflecting the mono product indications, should be substituted.*"

The clinical evaluator advised that the 5 mg/1000 mg strength should not be registered because the 5 mg strength of the dapagliflozin mono product is not registered in Australia.

The sponsor has responded that, for other FDC products that include metformin, it is the dose of metformin in the FDC that is being titrated and accidental overdosing is a significant safety issue. Therefore, patients should be advised to ensure that other supplies of metformin, as mono products or as FDC products, should not be used.



This would imply that a dose of dapagliflozin/metformin of 10 mg/2000 mg should not be obtained by using the 10 mg/1000 mg strength of Xigduo XR and a 1000 mg metformin XR tablet; however, three separate mono product tablets (1 x dapagliflozin 10 mg; 2 x metformin XR 1000 mg) could be used.

### **Risk management plan**

The Summary of ongoing safety concerns (Table 6 above) was noted.

The RMP evaluator requested that the following be added to “Important missing information”: malignancy, off-label use in obese patients who do not have T2DM, urosepsis, use in patients with BMI > 45. This is consistent with recommendations made in a recent RMP evaluation for the single ingredient dapagliflozin product Forxiga (PM-2013-01503-1-5).

The Delegate considered the RMP should be updated to include these additional types of missing information.

There are no post-registration studies proposed specifically for dapagliflozin and metformin FDC. Patients treated with dapagliflozin and metformin FDC will be included in the pharmacoepidemiology program described in the dapagliflozin RMP.

DECLARE (a multicentre trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events) is the post-registration trial for dapagliflozin. It has been designed so that, if there is no increased risk of cardiovascular events, the upper limit of 95%CI for major adverse cardiovascular events (MACE) will be < 1.30. DECLARE is also reporting on liver toxicity, bone fractures, nephrotoxicity, breast and bladder cancer, complicated genital infections, complicated UTIs, serious events related to hypovolaemia, and serious hypersensitivity reactions. It is due to report in 2020 for most outcomes; except for bladder and breast cancer, for which the due date for reporting is 2024.

Other post-marketing studies for dapagliflozin include studies evaluating: the risk of severe complications of UTI, risk of acute hepatic failure, risk of acute renal failure, risk of cancer, and extent of off-label use.

The OPR have recommended that one of the conditions of registration will be:

- Implement Dapagliflozin Metformin Fixed Dose Combination EU RMP (Version Number 3, Document date 16 October 2013, data lock point 1 May 2012) with Australia-specific Annex (Version Number 3, Document date 17 February 2014) and any future updates as a condition of registration.

Regarding periodic safety update reports (PSUR) for dapagliflozin, the TGA OPR has advised that approximately 22,000 patients have taken dapagliflozin across 36 countries. OPR commented that this was relatively slow uptake. Cases of renal failure, hypovolaemia, and life threatening UTIs were listed in the PSUR as being probably related to dapagliflozin. These can also be complications of diabetes.

### **Risk-benefit analysis**

#### **Delegate’s considerations**

The FDC of dapagliflozin and metformin is not irrational from a clinical point of view. Trials of use of the separate mono products, in combination, show a glucose lowering benefit. There are no Phase III trials of the FDC product; the sponsor has submitted bioequivalence studies of the separate mono products and the FDC product.



Relative to other treatments for diabetes, the combination of dapagliflozin and metformin does not cause weight gain. Hypoglycaemia can occur, but is not as prominent a concern as with sulphonylureas or insulin.

As expected from its mechanism of action, dapagliflozin is associated with reductions in weight and blood pressure. These changes might have benefits for patient morbidity and mortality, but these benefits were not specifically assessed in the dapagliflozin clinical development program.

The mono product PIs for both dapagliflozin and metformin have renal insufficiency (eGFR < 60 mL/min/1.73 m<sup>2</sup>) as a contraindication; as does the proposed FDC PI. This contraindication would apply to about one quarter of patients with T2DM at any point in time (that is, prevalent cases). Also, most patients with diabetes would eventually have eGFR < 60 mL/min/1.73 m<sup>2</sup>, at some point in the course of the disease (that is, lifetime risk).

For dapagliflozin, the contraindication for renal impairment (eGFR < 60 mL/min/1.73 m<sup>2</sup>) is based partly on the results of the Phase III trial in patients with moderate renal impairment (eGFR: 30-60 mL/min/1.73 m<sup>2</sup>), which did not show benefit over metformin on HbA1c (the 5 mg dose was assessed).

**Table 10: Study M102029. Effect on HbA1c in patients with moderate renal impairment**

Treatment	n	Baseline mean HbA1c (%)	LS mean change	LS mean difference compared to combination (95% CI)	p value
Dapagliflozin 5 mg + metformin	85	8.2	-0.44		
Dapagliflozin 5 mg	83	8.3	-0.41	-0.11 (-0.40, 0.17)	0.435
Metformin	84	8.5	-0.32	-0.08 (-0.37, 0.20)	0.561

n = number of subjects; LS = least squares

Dapagliflozin is also associated with concerns about volume contraction/depletion in patients with renal insufficiency and signals of increased serum creatinine from the clinical development program (although these were mostly transient).

For metformin, the contraindication for renal impairment (eGFR < 60 mL/min/1.73 m<sup>2</sup>) has a long history and is based on the fact that metformin is eliminated unchanged by kidney, combined with long-standing concerns about lactic acidosis, which has an incidence of about 3 per 100,000 person-years. All guidelines recommend ceasing metformin if eGFR < 30 mL/min/1.73 m<sup>2</sup>; however, guideline recommendations vary for eGFR 30-59 mL/min/1.73 m<sup>2</sup>. Some reviews have argued that the risk of lactic acidosis with metformin is no higher than the background (baseline) risk in patients with diabetes, multiple co-morbidities, and poly-pharmacy.

Besides volume contraction/depletion and increases in serum creatinine, other adverse reactions associated with dapagliflozin include genital mycotic infections and UTIs.

CV outcomes in the pre-marketing studies were unremarkable (DECLARE is the post-marketing study for dapagliflozin and will assess cardiovascular outcomes; among others.)

## Summary of issues

No Phase III trials have been conducted with the FDC tablet. The efficacy and safety of the FDC product is extrapolated from Phase III trials of co-administration of the separate mono products; and bioequivalence studies between the FDC product and the separate mono products.

The main issues for the FDC tablet are around:

- the wording of the indication
- the 5 mg/1000 mg strength (given 5 mg is not a registered strength for dapagliflozin mono product).

The Delegate planned to seek advice from the ACPM on the matters raised above.

## Proposed action

The Delegate had no reason to say, at this time, that the application for Xigduo XR should not be approved for registration.

Pending ACPM advice, the EU-style indication was proposed:

*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control for type 2 diabetes:*

- *in patients inadequately controlled on their maximally tolerated dose of metformin alone*
- *in combination with other glucose-lowering medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products (see CLINICAL TRIALS for different combinations)*
- *in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.*

## Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee address the following specific issues in particular:

1. Is the ACPM satisfied that the efficacy and safety of the FDC tablet (dapagliflozin/metformin-XR) has been established via the bioequivalence studies?
2. How much detail should be given in the indication? The sponsor is proposing, “*when treatment with both dapagliflozin and metformin is appropriate*”. This is a FDA-style indication. The EMA indication is: *in patients inadequately controlled on their maximally tolerated dose of metformin; in combination with other glucose lowering agents, including insulin ...; in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.*

Advice is sought on the wording of the indication for FDC anti-diabetic products in general; and also in this specific circumstance for Xigduo XR.

3. Advice is sought on whether the 5 mg/1000 mg tablet should be registered. A dose of 10 mg dapagliflozin and 2000 mg metformin could be obtained by taking two of these FDC tablets (2 x 5/1000) or by taking three separate mono product tablets (1 x dapagliflozin 10 mg; 2 x metformin XR 1000 mg).

## Response from Sponsor

### Introduction

The sponsor acknowledges the comments of the evaluators and the Delegate that the submission package supports registration of the Xigduo XR (dapagliflozin/metformin HCl) FDC as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both dapagliflozin and metformin is appropriate. The sponsor wishes to take this opportunity to provide additional comments in relation to the Delegate's specific request for ACPM advice.

*Delegate's Question 1 for ACPM: Is the ACPM satisfied that the efficacy and safety of the FDC tablet (dapagliflozin/metformin XR) has been established via the bioequivalence studies?*

**Sponsor's comment:** The sponsor considers the clinical development programme for the FDC to have satisfactorily established that the proposed Xigduo XR tablets are as efficacious and well tolerated as the mono components, dapagliflozin and metformin taken together, based on existing Phase III trials using the mono components in conjunction with the biopharmaceutical studies that demonstrated bioequivalence of the individual mono components with the FDC.

The clinical programme supporting this submission consisted of 8 Phase III, randomised, controlled, double-blind clinical studies that were previously used to support the approval of dapagliflozin (Forxiga). Seven studies had a short term (ST) period of 24 weeks duration (MB102014, D1690C00012, MB102034, MB102021, D1690C00010, D1690C00006 and MB102013), while D1690C00004 had a short term period of 52 weeks. Completed long term extension periods of these studies provide data up to 104 weeks in duration. The results from these trials demonstrate the use of dapagliflozin in combination with metformin is an efficacious and well tolerated treatment option for patients with T2DM. There were no safety issues specific to the combination of dapagliflozin with metformin XR, compared to the mono components alone.

The Phase III programme for dapagliflozin was conducted using co-administration of the individual components of dapagliflozin and metformin. Hence, it was necessary to bridge from the co-administration of the mono component tablets to the FDC. In order to achieve this bridging, three relative bioavailability studies, two bioequivalence studies, and one local bioequivalence study were conducted. As the Phase III add-on to metformin studies used US sourced Glucophage, it was necessary to demonstrate its bioequivalence to the Australian metformin formulations, Diabex. Additionally, the dapagliflozin clinical programme used metformin immediate release (IR) and/or XR. These aspects were taken into consideration when designing the FDC-specific biopharmaceutical studies.

Relative bioavailability/bioequivalence (BA/BE) studies showed that the Xigduo XR tablets are bioequivalent to the individual dapagliflozin and metformin XR tablets administered together, and that the metformin XR component (US-sourced Glucophage) was bioequivalent to the Australian-sourced metformin XR formulation, Diabex XR. Therefore, these BA/BE studies bridge the co-administration of the individual components to the Xigduo XR tablet. Additionally, the Australia-sourced IR reference product (Diabex) was shown to be bioequivalent to the metformin IR formulation (US-sourced Glucophage) used in the dapagliflozin Phase III clinical development programme. Literature evidence supports that metformin XR is therapeutically equivalent to metformin IR (Fujioka et al 2003<sup>9</sup>), and the Diabex XR PI further supports the switching of patients using metformin IR to metformin XR. Taken together, studies conducted using co-administration of the individual components of dapagliflozin and metformin IR/XR (administered as Glucophage) are considered to be relevant to this Xigduo XR submission.

<sup>9</sup> Fujioka K et al. Glycemic control in patients with Type 2 diabetes mellitus switched from twice-daily immediate release metformin to a once-daily extended release formulation. *Clin Ther* 2003;25:515-529

On the basis of the result of the biopharmaceutic program, the clinical evaluator concluded that Australian patients switching to the Xigduo XR product from the same strengths of dapagliflozin plus Diabex XR mono products can be expected to have equivalent systemic exposures to both analytes from the FDC tablet. Likewise, patients taking Diabex XR who are adding dapagliflozin to their treatment regime can be expected to have equivalent systemic exposures to metformin from Xigduo XR.

The equivalence of the mono components with the FDC tablet taken together with the safety and efficacy established during the Phase III studies conducted using co-administration of the individual components of dapagliflozin and metformin IR/XR reasonably suggests that the efficacy and safety of the proposed FDC has been adequately demonstrated. Furthermore it should be noted that the approach taken for the development of the Xigduo XR tablets is commonplace when developing FDC products.

*Delegate's Question # for ACPM: How much detail should be given in the indication? The sponsor is proposing, "when treatment with both dapagliflozin and metformin is appropriate". This is a FDA-style indication. The EMA indication is: in patients inadequately controlled on their maximally tolerated dose of metformin; in combination with other glucose lowering agents, including insulin ...; in patients already being treated with the combination of dapagliflozin and metformin as separate tablets." Advice is sought on the wording of the indication for FDC anti-diabetic products in general; and also in this specific circumstance for Xigduo XR.*

**Sponsor's comment:** The sponsor considers the current proposed indication, amended to reference the *Clinical Trials* and *Precautions* sections, is appropriate:

*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate (see Clinical Trials and Precautions for available data on the combination therapy).*

The PI adequately describes the clinical settings where the combination can be used (including initial combination). Furthermore, this approach for simplifying the indication is consistent with that proposed by the TGA on March 7, 2014, for the Forxiga submission subsequently approved on April 30, 2014. This succinct indication is also consistent with the Invokana PI add-on to antidiabetic agents indication. The *Clinical Trials* section of the proposed PI provides the details of the clinical use of the components of Xigduo XR, dapagliflozin and metformin, including combination with a DPP4 or insulin in combination with other OADs. This is consistent with the approved dapagliflozin mono product PI. The PI also includes the pertinent safety information relevant to both components such that the prescriber is aware of instances where the FDC is not appropriate due to limitations posed by either dapagliflozin or metformin. Additionally the *Dosage and Administration* section of the PI also includes dosing instructions for the FDC in all approved indications for concomitant administration of dapagliflozin and metformin. Consequently, the sponsor considers that taken in conjunction with the remainder of the PI, the proposed indication is appropriate.

*Delegate's Question 3 for ACPM: Advice is sought on whether the 5 mg/1000 mg tablet should be registered. A dose of 10 mg dapagliflozin and 2000 mg metformin could be obtained by taking two of these FDC tablets (2 x 5/1000) or by taking three separate mono product tablets (1 x dapagliflozin 10 mg; 2 x metformin XR 1000 mg).*

**Sponsor's comment:** During development of the presentations for the FDC tablet the sponsor was mindful of the fact it is the dose of metformin in the Xigduo XR FDC that is being titrated and accidental overdosing is a significant safety issue. Consequently, the presentations developed are aimed to facilitate the delivery of a 10 mg dapagliflozin dose with the appropriate dose of metformin based on a patients requirements without the need to "mix and match" different of the FDC presentations or combine a FDC tablet with a

separate metformin extended release tablet. This is consistent with ACPM Resolution regarding fixed dosed medicinal products containing metformin from October 2010 and the dosage and administration advice in the approved PI for metformin extended release tablets such as Diabex XR which states: “*The combined use of different strengths of Diabex XR 500, Diabex XR 750 or Diabex XR 1000 is not recommended. Only one strength (Diabex XR 500, Diabex XR 750 or Diabex XR 1000) should be used at a time in order to avoid accidentally exceeding the recommended upper daily dose limit of 2000 mg.*”

The Xigduo XR 5/1000 tablet is proposed to be able to deliver the maximum dose of metformin XR (2000 mg) and the approved dose of dapagliflozin (10 mg) when two tablets are taken together as a single dose. A single tablet to administer dapagliflozin 10 mg/2000 mg metformin is not feasible due to the fact that the size of the tablets required accommodate such a dose would prove difficult to swallow resulting in poor patient acceptance thereby defeating the purpose of a FDC. Xigduo XR 5/1000 is not intended for administration as a single tablet as is clearly indicated in the proposed PI.

The Delegate has suggested instead of the administration of two Xigduo XR 5/1000 tablets, three separate mono product tablets (1 x dapagliflozin 10 mg; 2 x metformin XR 1000 mg) could be used. While this is true, the sponsor contends that the proposed FDC offers a means of simplification of treatment and improved and convenience of therapy with a reduced tablet burden leading to improved patient compliance. Adherence to therapy is especially important for the management of chronic diseases such as diabetes, but the need for multiple antidiabetic medications to achieve and then sustain adequate HbA1c control often leads to poor adherence. Recent reviews indicate that levels of non-adherence in patients with T2DM range from 10% to 30% (Blaschke et al 2012<sup>10</sup>; Cramer 2004<sup>11</sup>; Schernthaner 2010<sup>12</sup>; Skaer et al 1993<sup>13</sup>; Venturini et al 1999<sup>14</sup>). Poor adherence leads to inadequate glycaemic control and subsequently increased risk of associated complications. FDC therapy offers the potential to reduce the pill burden for patients, and clinical evidence from studies of diabetes and other chronic diseases indicates that FDC therapy can result in improvements in patient adherence. The use of FDC therapy reduced the risk of non-adherence by 24% to 26% compared with free-drug combination regimens in a meta-analysis of patients with a range of chronic medical conditions, including diabetes and hypertension (Bangalore et al 2007<sup>15</sup>).

Patients in a retrospective managed care database study who switched from monotherapy or polytherapy for T2DM to a single FDC tablet improved their adherence by 23% and 16%, respectively (Melikian et al 2002<sup>16</sup>). Similarly, a retrospective database analysis of 16,928 patients with T2DM indicated that switching from dual therapy to rosiglitazone-metformin FDC therapy resulted in a statistically significant improvement in adherence rate (Vanderpoel et al 2004<sup>17</sup>). Therefore, the sponsor considers simplification of therapy

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<sup>10</sup> Blaschke T et al. Adherence to Medications: Insights Arising from Studies on the Unreliable Link Between Prescribed and Actual Drug Dosing Histories. *Ann Rev Pharmacol Toxicol.* 2012;52;275-301.

<sup>11</sup> Cramer JA. A systematic review of adherence with medications for diabetes. *Diab Care* 2004;27;1218-1224.

<sup>12</sup> Schernthaner G. Fixed-dose combination therapies in the management of hyperglycaemia in Type 2 diabetes: an opportunity to improve adherence and patient care. *Diabetic Med* 2010;27;739-743

<sup>13</sup> Skaer TL et al: Effect of value-added utilities on prescription refill compliance and Medicaid health care expenditures - a study of patients with non-insulin-dependent diabetes mellitus. *J Clin Pharm Ther* 1993; 18(4);295-299.

<sup>14</sup> Venturini F et al. Compliance with sulfonylureas in a health maintenance organization: a pharmacy record-based study. *Annals Pharmacotherapy* 1999;33;281-288.

<sup>15</sup> Bangalore et al. Fixed dose combinations improve medication compliance: a meta analysis. *Am J Med* 2007;120;713-719.

<sup>16</sup> Melikian C et al. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed dose combination therapy. *Clin Ther* 2002;3(24);460-467.

<sup>17</sup> Vanderpoel DR et al. Adherence to a fixed dose combination of rosiglitazone maleate/metformin hydrochloride in subjects with type 2 diabetes: a retrospective database analysis. *Clin Ther* 2004;26;2066-2075

provided by the Xigduo XR 5/1000 tablet to deliver the maximum dose of metformin together with dapagliflozin important gaining the benefits associated with improvements in patient adherence and improved control of HbA1c.

### **Conclusion**

The sponsor considers Xigduo XR to provide a valuable treatment option for physicians as it provides a combination of drugs with complementary mechanisms of action, and with clinically important effects on HbA1c, FPG, PPG and weight loss. As such, it is expected to form a clinically relevant paradigm for achieving and maintaining glycaemic control in patients with T2DM when treatment with both dapagliflozin and metformin is appropriate, including initial combination therapy, or in combination with DPP4 or insulin in combination with other oral antidiabetic drugs, as described in the clinical trials section of the PI. Many patients with T2DM do not achieve satisfactory glycaemic control with a single agent and there is a need for effective combination therapy options. A FDC product will offer the advantage of increased dosing convenience and may potentially improve compliance for those patients who can benefit from combination therapy with dapagliflozin and metformin.

### **Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new combination of active ingredients.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Xigduo XR fixed dose extended release film coated tablets, containing 10 mg/500 mg of dapagliflozin/metformin hydrochloride, 10 mg/1000 mg of dapagliflozin/metformin hydrochloride and 5 mg/1000 mg of dapagliflozin/metformin hydrochloride as new combinations of active ingredients, to have an overall positive benefit-risk profile for the indication;

*As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.*

*Individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of dapagliflozin 10 mg and metformin extended release 2000 mg.*

### **Proposed conditions of registration:**

The ACPM agreed with the Delegate on the proposed conditions of registration.

### **Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:**

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

### **Specific advice:**

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. Is the ACPM satisfied that the efficacy and safety of the FDC tablet (dapagliflozin/metformin-XR) has been established via the bioequivalence studies?

The ACPM advised that the efficacy and safety of the FDC tablet had been adequately established via the bioequivalence studies.

2. How much detail should be given in the *indication*? The sponsor is proposing, “*when treatment with both dapagliflozin and metformin is appropriate*”. This is a FDA-style indication. The EMA indication is: “*in patients inadequately controlled on their maximally tolerated dose of metformin; in combination with other glucose lowering agents, including insulin ...; in patients already being treated with the combination of dapagliflozin and metformin as separate tablets*”. Advice is sought on the wording of the indication for FDC anti-diabetic products in general and also in this specific circumstance for XIGDUO.

The ACPM advised that, in general, indications which are simpler and more consistent support improved management choices. On balance, the ACPM advised the sponsor’s proposal of “*when treatment with both dapagliflozin and metformin is appropriate*” is sufficient.

3. Advice is sought on whether the 5 mg/1000 mg tablet should be registered. A dose of 10 mg dapagliflozin and 2000 mg metformin could be obtained by taking two of these FDC tablets (2 x 5/1000) or by taking three separate mono product tablets (1 x dapagliflozin 10 mg; 2 x metformin-XR 1000 mg).

The ACPM advised that the 5 mg/1000 mg tablet should be available for ‘two at once’ dosing, but not twice daily or once daily dosing.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xigduo XR 10/500 dapagliflozin 10 mg (as propanediol monohydrate) / metformin hydrochloride 500 mg modified release tablets blister pack; Xigduo XR 10/1000 dapagliflozin 10 mg (as propanediol monohydrate) / metformin hydrochloride 1000 mg modified release tablets blister pack; and Xigduo XR 5/1000 dapagliflozin 5 mg (as propanediol monohydrate) / metformin hydrochloride 1000 mg modified release tablets blister pack, indicated for:

*Xigduo XR is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate (see Clinical Trials and Precautions for available data on the combination therapy).*

## Specific conditions of registration applying to these goods

- The Dapagliflozin Metformin Fixed Dose Combination EU Risk Management Plan (RMP) Version 3 dated 16 October 2013 [data lock point (DLP) 1 May 2012] and Australia Specific Annex Version 3 dated 17 February 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The results of any further studies of dapagliflozin and metformin should be provided to the TGA as soon as they become available.

## Attachment 1. Product Information

The Product Information approved for Xigduo XR at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

## **Attachment 2. Extract from the Clinical Evaluation Report**



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