Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Dapagliflozin (as propanediol monohydrate) / Metformin hydrochloride

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

Sponsor: AstraZeneca Pty Ltd

First Round CER: 15 December 2013
Second Round CER: March 2014

TGA Health Safety Regulation

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Abbreviation	Meaning
ACEI	Angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin II type 1 receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration curve
$AUC_{(INF)}$	Area under the curve extrapolated to infinity
$AUC_{(0\text{-}T)}$	Area under the curve extrapolated from time zero to the time of the last quantifiable concentration
BA	Bioavailability
BD/BID	Twice daily
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
CK	Creatine kinase
C_{max}	Maximum plasma drug concentration
CrCl	Creatinine clearance
CSR	Clinical study report
CTD	Common technical document
CV	Cardiovascular

Abbreviation	Meaning
Dapa/Met	Dapagliflozin/Metformin
DBP	Diastolic blood pressure
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration (USA)
FDC	Fixed dose combination
FPG	Fasting plasma glucose
HbA1c	Haemoglobin A1c
IDF	International Diabetes Federation
IR	Immediate release
LOCF	Last observation carried forward
LT	Long-term
LT1	Long term 1 extension period
LT2	Long term 2 extension period
OAD	Oral antidiabetic drug
PD	Pharmacodynamic
PI	Product Information
PK	Pharmacokinetic
PPG	Postprandial glucose
PT	Preferred term
QAM	Once daily in the morning
QD	Once a day; Once daily
QPM	Once daily in the evening
RMP	Risk Management Plan
SAE	Serious adverse event

Abbreviation	Meaning
SBP	Systolic blood pressure
SGLT2	Sodium-dependent glucose co-transporter 2
SI	International System of Units
ST	Short-term
ST+LT	Short-term plus long-term
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UTI	Urinary tract infection
XR	Extended release

1. Introduction

This is a full submission to register and new fixed combination product.

Xigduo XR is a combination product consisting of dapagliflozin which is a reversible competitive inhibitor of sodium glucose co-transporter (SGLT2) and metformin is a biguanide, which is an oral antidiabetic drug.

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

Comment: The submission also includes the following strength: 5 mg dapagliflozin/500 mg metformin HCl extended-release) 5 mg/500 mg tablets.

Module 2.5 states "*As dapagliflozin 10 mg QD is the only recommended dose of dapagliflozin in Australia, the 5 mg/500 mg Dapa/Met 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.*"

2. Clinical rationale

Type 2 diabetes mellitus (T2DM) 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 oral antidiabetic drug (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 sodium-dependent glucose co-transporter 2 (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 haemoglobin A1c (HbA1c). Dapagliflozin's mechanism of action is complementary to most other glucose lowering drugs.

Metformin hydrochloride (metformin) is a well-characterised oral antidiabetes drug which has been in widespread use for decades and is the first-line agent of choice for T2DM. Metformin lowers HbA1c, fasting plasma glucose (FPG), and postprandial glucose (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 Dapa/Met XR fixed dose combination (FDC) product offers a simplification and convenience of therapy, with once daily administration with (or after) the evening meal, thereby improving patient compliance.

2.1. 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

3. Contents of the clinical dossier

3.1. Scope 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 1:

- Application letter, application form, draft Australian PI and CMI

Module 2:

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

3.2. Paediatric data

The submission did not include paediatric data. A waiver was granted in Europe on the basis that the fixed dose combination offers no benefit over the free combination of dapagliflozin and metformin tablets in the paediatric population.

3.3. 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/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.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The applicant provided only bioavailability and bioequivalence studies in this submission. 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[1]) between dapagliflozin and metformin was submitted in the initial dapagliflozin application and has shown no clinically meaningful effect of dapagliflozin on metformin pharmacokinetics and vice versa.

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	Bioavailability	MB102060	BA: met XR vs Glucophage XR
		MB102065	BA: FDC dapa/met XR vs Glucophage XR
		MB102071	BA: FDC dapa/met XR vs Glucophage XR
	Bioequivalence† - Single dose	MB 102092	BE: FDC dapa/met vs dapa + Glucophage XR
		MB 102100	BE: FDC dapa/met vs dapa + Glucophage XR – effect of food
		CV181120	BE: Glucophage vs Diabex
	Bioequivalence† - Multi dose	MB 102092	BE: FDC dapa/met vs dapa + Glucophage XR

[1] Evaluated in the original submission for dapagliflozin PM-2010-03812-3-5

PK topic	Subtopic	Study ID	Primary aim
		MB102125	BE: FDC dapa/met vs dapa + Diabex XR
		MB 102100	BE: FDC dapa/met vs dapa + Glucophage XR – effect of food
	Food Effect	MB 102100	BE: FDC dapa/met vs dapa + Glucophage XR – effect of food
		CV181120	BE: Glucophage vs Diabex
PK in target patient population	Timing of dosing	MB102013b	PD: Morning vs evening dosing

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

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

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

Three relative bioavailability (BA) studies, 3 bioequivalence (BE) and one Australia specific BE study were conducted for the dapa/met XR FDC development programme.

4.2.1.1. Bioavailability

4.2.1.1.1. Bioequivalence of clinical trial and market formulations

Study MB102060 characterised the relative bioavailability of a prototype tablet containing 1,000 mg metformin XR relative to two 500 mg Glucophage XR tablets (the current method of obtaining a 1,000 mg dose of Glucophage XR). To obtain a similar in vivo performance of this metformin only prototype to a future FDC, this prototype contained a placebo to reflect the size and inactive constituents of an FDC dapagliflozin and metformin XR tablet formulation. The results of this study indicated that further development of the metformin XR core for the dapa/met XR FDC was feasible.

Studies MB102065 and MB102071 characterised the relative bioavailability of two prototype tablets of dapa/met XR 10 mg/1000 mg and 10 mg/500 mg, respectively, relative to the individual components of dapagliflozin and metformin XR (Glucophage XR) in healthy subjects. These studies enabled formulation selection for further development.

Two studies using the to be marketed formulation (same embossing, colour, and commercial scale manufacturing lot size and site as the proposed commercial formulations) were conducted to evaluate bioequivalence, food effect and steady state pharmacokinetics of the 10 mg/1000 mg XR FDC tablet (Study MB102092) and the 5 mg/500mg XR FDC tablet (Study MB102100). These studies demonstrated that in the fed state dapa/met XR FDC tablets (10 mg/1000 mg and 5 mg/500 mg respectively) were bioequivalent to the co-administration of the individual components of dapagliflozin and metformin XR (US sourced Glucophage XR) in healthy subjects.

The 90% CI of the ratios of geometric least squares means for dapagliflozin and metformin Cmax, $AUC_{(0-T)}$, and $AUC_{(INF)}$, were entirely contained within 0.80 to 1.25.

These studies also investigated the effect of food (see below) and also characterised the steady state pharmacokinetics.

4.2.1.1.2. Bioequivalence to relevant registered products

The formulations of metformin IR and XR marketed in Australia (Diabex and Diabex XR) are not the same as the marketed formulations used in the efficacy studies (Glucophage IR or XR) or in the bioequivalence studies discussed above. To address these issues two studies were done to compare the bioequivalence of the proposed FDC tablets to the marketed products in Australia.

Study MB102125 demonstrated that in the fed state, dapa/met XR FDC tablets (10 mg/1000 mg and 5 mg/500 mg, respectively) were bioequivalent to the co-administration of the individual components of dapagliflozin and Australian sourced Diabex XR to healthy subjects.

In the 5 mg/500 mg XR evaluation cohort, two subjects appeared not to have been dosed in Period 2 of the study. One subject was randomised to the reference treatment (individual components) and the other to the 5 mg/500 mg XR FDC. The reason for the missed dose could not be documented but subject non-compliance could not be ruled out. Analysis was conducted including and excluding these subjects with the analysis excluding these subjects considered the primary analysis. When these subjects were included the bioequivalence criteria were not met, albeit by very small margins (<2%).

The remaining 2 FDC strengths not studied clinically (5 mg/1000 mg and 10 mg/500 mg are the subject of an in vivo biowaiver application included in the submission (see Section 4.2.1.1.6 below).

In addition, Study CV181120 demonstrated that the Australia sourced immediate release (IR) 500 mg and 1,000 mg reference product (Diabex) is bioequivalent to the relative strengths of metformin IR formulation (US sourced Glucophage) used in the clinical efficacy studies.

4.2.1.1.3. Influence of food

The effect of food was investigated in Studies MB102092 and MB102100. Compared to the fasted state, a light meal decreased the Cmax of dapagliflozin by 35% when administered as the FDC tablet and did not have an effect on $AUC_{(0-T)}$ and $AUC_{(INF)}$ of dapagliflozin in the FDC. These findings were very similar to the effect of food on the dapagliflozin monotherapy tablet.

A standard meal did not appear to have an effect on Cmax, $AUC_{(0-T)}$ and $AUC_{(INF)}$ of metformin in the FDC compared to the fasted state.

4.2.1.1.4. Steady state pharmacokinetics

The steady state pharmacokinetics were also investigated in Studies MB102092 and MB102100. The results from the metformin single and steady state fed plasma concentration time profiles showed no propensity for “dose dumping” for the 500 mg or 1000 mg metformin XR component of the FDC formulations. The metformin XR components of the 10 mg/500 mg and 5 mg/1000 mg dapa/met XR FDC formulations are the same as the metformin XR components in the 5 mg/500 mg and 10 mg/1000 mg dapa/met XR FDC formulations not clinically studied.

4.2.1.1.5. Effect of administration timing

One efficacy study (MB102013) evaluated in the original submission, was conducted to investigate the effect of evening dosing rather than morning dosing of dapagliflozin. This was undertaken to align the XR FDC tablets with the approved recommended dosing for metformin XR of once daily in the evening. The study found that following treatment with dapagliflozin, there were no meaningful differences in adjusted mean change from baseline in HbA1c, FPG or total body weight at week 24 between the QAM and QPM treatment groups at the same dose level, and reductions in HbA1c and FPG remained consistent for the dapagliflozin 10 mg QAM

and QPM treatment groups until week 102. The conclusion was: "with pm dosing HBA1c fell to a similar extent (0.73-0.86%, different from placebo 0.56-0.61%) in all three dapagliflozin dosage groups" ([previous dapagliflozin Clinical Evaluation Report]).

4.2.1.1.6. In vivo waiver for FDC strengths not studied clinically

Both dapagliflozin 5 mg and 10 mg layers of the FDCs are not compositionally proportional, nor are the 500 mg and 1,000 mg metformin XR layers. The bioequivalence studies used the lowest and the highest strengths of both components (5 mg/500 mg and 10 mg/1,000 mg). An in vivo waiver is requested for the two middle strengths (10 mg/500 mg and 5 mg/1,000 mg). In accordance with the Australian Guidelines (Australian Regulatory Guidelines for Prescription Medicines – Biopharmaceutic Studies 2004), the waiver is requested based on:

- Linear pharmacokinetics of dapagliflozin from 0.01 mg to 500 mg
- Demonstration of bioequivalence of both the dapa/met 5 mg/500 mg and the 10 mg/1,000 mg XR strengths of the FDC to the individual monotherapy tablets administered concomitantly (Studies MB102092, MB102100 and MB102125)
- The product being manufactured by the same manufacturing process and the composition of the strengths being qualitatively and quantitatively similar or proportional and hence can be considered to be "formulation proportional"
- Comparable in vitro dissolution profiles with regard to dapagliflozin and metformin for the respective dapa/met XR FDC strengths throughout the physiological pH range.

On the basis of the reasons given above this request for waiver appears acceptable.

4.2.2. Pharmacokinetic interactions

A 2-way drug-drug interaction study (Study MB102026) between dapagliflozin and metformin was submitted in the initial dapagliflozin dossier [evaluated previously for the application to register dapagliflozin PM-2010-03812-3-5], and showed "no effect on the pharmacokinetics of metformin and no effect of metformin on the pharmacokinetics of dapagliflozin" (Clinical Evaluation Report).

4.3. Evaluator's overall conclusions on pharmacokinetics

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

The Australia-specific pivotal BE 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 (i.e., the 90% CIs of the ratios of geometric least square means for dapagliflozin and metformin Cmax, $AUC_{(0\text{-}T)}$, 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 BE 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 Cmax of dapagliflozin by about 34%, but did not affect $AUC_{(0\text{-}T)}$ 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 Cmax is unlikely to have a clinically meaningful effect on dapagliflozin's efficacy. Thus the effect of food on dapagliflozin Cmax is not considered clinically meaningful. A light-fat meal did not appear to have an effect on Cmax, $AUC_{(0\text{-}T)}$, 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 dapa/met XR FDC at steady state (Studies MB102025, MB102092 and MB102100).

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

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

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

5.2. Summary of pharmacodynamics

The information in the following summary is derived from the Module 2 summaries.

5.2.1. Mechanism of action

Dapagliflozin was the first in a new class of compounds that inhibits the renal sodium dependent glucose co-transporter 2 (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, 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 reductions. Furthermore, due to its insulin independent mechanism of action, dapagliflozin is associated with a low risk of hypoglycaemia.

Metformin hydrochloride (metformin) is a well characterised oral antidiabetic drug which has been in widespread use for decades and is the first line agent of choice for T2DM. Metformin lowers HbA1c, fasting plasma glucose (FPG) and postprandial glucose 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.

5.3. Evaluator's overall conclusions on pharmacodynamics

No new data was submitted related to pharmacodynamics.

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

The justification of the inclusion of the 5 mg/1000 mg dapa/met 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 dapa/met XR 10 mg/2000 mg.

7. Clinical efficacy

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

7.1. Type 2 diabetes mellitus. Pivotal efficacy studies

Eight clinical efficacy studies were submitted in support for this application. All had been previously evaluated in the original dapagliflozin application (PM-2010-03812-5) and the application for extension of indication and changes to PI (PM-2013-01503-1-5). Clinical Studies which were previously evaluated were not evaluated again. Reference is made to the clinical evaluation reports for these submissions.

New data for one study was submitted in this application – new long term data was submitted for Study D1690C00012. This data has been evaluated in section 7.1.1.

Summaries of all pivotal efficacy studies are tabulated in Section 7.1.2.

7.1.1. Study D1690C00012

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 Type 2 Diabetes Mellitus who have Inadequate Glycaemic Control on Metformin Alone.

7.1.1.1. Study design, objectives, locations and dates

International, multicentre, randomised, double blind, placebo controlled, parallel group study conducted at 40 centres in 5 countries (Bulgaria, Czech Republic, Hungary, Poland, Sweden) from February 2009 to December 2011.

Primary objective: to assess the same objectives as for the 24 week short term treatment period after 102 weeks of double blind treatment:

- Change in total bod 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 ≥5% from baseline to week 102

Secondary objectives:

- To assess the effect of Dapagliflozin 10 mg daily in combination with metformin compared to placebo in combination with metformin after 50 and 102 weeks of double blind treatment on:
- Bone mineral density (BMD) at lumbar spine (L1-4), femoral neck, and total hip as measured by dual energy w-ray absorptiometry
- Biochemical markers of bone formation and bone resorption
- To evaluate the safety and tolerability by assessment of adverse events, laboratory values, ECG, pulse, blood pressure, hypoglycaemic events, calculated creatinine clearance and physical examination findings after 102 weeks of treatment

7.1.1.2. Inclusion and exclusion criteria

7.1.1.2.1. Inclusion

- Male patients aged ≥40 and ≤75 years and females (post-menopausal or had hysterectomy for at least 5 years) aged ≥55 and ≤75 years
- Diagnosed with T2DM and treated with metformin monotherapy on a stable dose of ≥1,500 mg/day for at least 12 weeks prior to treatment
- Demonstrated inadequate glycaemic control, defined as HbA1c ≥6.5% and ≤8.5%
- BMI ≥25 kg/m2
- Body weight ≤120 kg
- Fasting plasma glucose ≤13.2 mmol/L at the start at randomisation

7.1.1.2.2. Exclusion

- Type 1 diabetes, diabetes insipidus, corticosteroid-induced type 2 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketonic coma, or known condition of congenital renal glucosuria
- Previous participation in a clinical trial with dapagliflozin
- Symptoms of poorly controlled diabetes that would preclude participation in this trial including but not limited to marked polyuria and polydipsia with greater than 5% weight loss during the 3 months prior to enrolment, or other signs and symptoms
- Any ongoing oral anti-diabetic treatment apart from metformin or treatment with chronic insulin within 24 weeks prior to Visit 1 (however, one temporary period of daily insulin injections no longer than 7 days was allowed)
- Administration of weight-loss medication, including but not limited to sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine within 30 days prior to enrolment
- Administration of treatment known to significantly influence bone metabolism, including but not limited to bisphosphonate, calcitonin, replacement or chronic systemic treatment with corticosteroids, or hormone replacement therapy (HRT) within 6 months prior to enrolment
- Body weight change >5% within 3 months prior to enrolment
- Severe uncontrolled hypertension defined as systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg
- T-score <-2.0 for BMD at lumbar spine (L1-4), femoral neck, or total hip at baseline DXA measurement

- Vitamin D deficiency (25-hydroxyvitamin D level <12 ng/mL [<30 nmol/L])
- Aspartate aminotransferase (AST) >3 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3 x ULN, or serum total bilirubin (TBL) >34 µmol/L (>2 mg/dL)
- Creatine kinase (CK) >3 x ULN
- Haemoglobin ≤105 g/L (≤10.5 g/dL) for men, haemoglobin ≤95 g/L (≤9.5 g/dL) for women
- Urine albumin to creatinine ratio >1800 mg/g (>203.4 mg/mmol)
- Renal failure or renal dysfunction (creatinine clearance using Cockcroft and Gault formula <60 mL/min) or serum creatinine ≥133 µmol/L (≥1.5 mg/dL) for male subjects and ≥124 µmol/L (≥1.4 mg/dL) for female subjects
- Thyroid-stimulating hormone (TSH) values outside normal range
- Significant cardiovascular history within the past 6 months prior to the enrolment visit (myocardial infarction, unstable angina, transient ischemic attack, unstable or previously undiagnosed arrhythmia, unstable chronic heart failure, cardiac surgery, or revascularisation)
- History of bariatric surgery
- History of metabolic bone disease or disease known to significantly influence bone metabolism (e.g., Cushing's syndrome, Paget's disease, hyperthyroidism, hyperparathyroidism, or hypogonadism other than menopause)
- History of osteoporotic fracture, bilateral hip replacement, spinal deformity, or spinal surgery
- History of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin carcinoma or in-situ carcinoma of the cervix
- History of unstable or rapidly progressing renal disease
- History of chronic haemolytic anaemia, with the exception of sickle cell trait or thalassemia minor
- Severe hepatic disease including chronic active hepatitis and positive serologic evidence of current infectious liver disease including subjects being positive for hepatitis B viral antibody immunoglobulin M, hepatitis B surface antigen, and hepatitis C virus antibody

7.1.1.3. Study treatments

Patients were administered dapagliflozin 10 mg or matching placebo as add-on therapy to metformin during the ST (24 weeks) and LT (78 weeks) periods. Patients were instructed to take the study medication orally once daily in the morning, immediately before or together with a meal.

The metformin was open label at a dose of 1,500, 2,000 or 2,500 mg/day during the ST and LT periods, based on their metformin dose during the last 12 weeks prior to enrolment. Metformin was taken just before or together with a meal.

7.1.1.4. Efficacy variables and outcomes

The primary efficacy outcomes were:

- 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 ≥5% from baseline to week 102

7.1.1.5. Randomisation and blinding methods

Randomisation was stratified by gender to ensure neither gender could exceed 60%. Dapagliflozin and matching placebo were double blinded. Metformin was open label.

7.1.1.6. Analysis populations

Full analysis set: includes all randomised subjects (as randomised) who received at least 1 dose of double-blind study medication, who had a non-missing baseline value and at least 1 post-baseline efficacy value for at least 1 efficacy variable to be analysed.

ST + LT1 completers analysis set: consists of all subjects in the full analysis set who did not receive rescue medication during the ST + LT1 period, completed the ST + LT1 period and entered the LT2 period. It is a subset of the full analysis set.

Safety analysis set: consists of all subjects who received at least 1 dose of double-blind study medication.

7.1.1.7. Sample size

Sample size considerations were only performed for the primary efficacy endpoint and the MR sub-study at week 24 and for the percent change in BMD at lumbar spine (L1-4) from baseline to week 50.

7.1.1.8. Statistical methods

All long term efficacy analyses were considered exploratory. In general, the last observation carried forward (LOCF) method was not used. Continuous efficacy variables were analysed using a longitudinal repeated measures analysis with the fixed categorical effects of treatment, week and treatment by week interaction, and gender as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Rescue was added as an additional effect in the model for analyses including rescued patients.

The model provided least squares estimates, standard errors, and 2 sided 95% CI for mean change from baseline to all post baseline time points within treatment groups and for differences between the dapagliflozin treatment groups versus placebo. No p-values for treatment group comparisons were calculated. The methodology of Zhang, Tsiatis, and Davidian and Tsiatis, Davidian, Zhang and Lu with adjustment for baseline value and gender was used to analyse proportions. Subjects discontinued or missed measurements (regardless type of missing) at the specified time point were considered not achieving the specified response. BMD and bone markers were analysed using a longitudinal repeated measures analysis with the fixed categorical effects of treatment, week and treatment by week interaction, and gender as well as the continuous fixed covariates of baseline measurement and baseline measurement by week interaction.

For the longitudinal repeated measures analyses of BMD, the logarithms of post baseline and baseline measurements were used. For analyses by strata (male and female) the model excluded gender. The model was used to derive least squares estimates, standard errors and 2 sided 95% CI for mean (percent) change from baseline to all post baseline time points within treatment groups and for differences between the dapagliflozin treatment group versus placebo. Further, nominal p-values for treatment group comparisons were calculated. Comparisons between treatment groups in proportions were performed using the methodology of Zhang, Tsiatis, and Davidian and Tsiatis, Davidian, Zhang and Lu with adjustment for baseline value and gender. For these analyses, the LOCF approach was used.

7.1.1.9. Participant flow

Table 2: Study D1690C00012: Participant flow

	Placebo + met	Dapa 10mg + met	Total
Subjects	91	91	182
Subjects completing the study (%)	71 (78.0)	69 (75.8)	140 (76.9)
Subjects not completing the study (%)	20 (22.0)	22 (24.2)	42 (23.1)
Reason for not completing the study (%)			
Adverse event	0	4 (4.4)	4 (2.2)
Subject no longer meets study criteria	13 (14.3)	11 (12.1)	24 (13.2)
Subject withdrew consent	3 (3.3)	6 (6.6)	9 (4.9)
Poor/non-compliance	3 (3.3)	0	3 (1.6)
Death	0	1 (1.1)	1 (0.5)
Administrative reason by sponsor	1 (1.1)	0	1 (0.5)

Met = metformin; dapa = dapagliflozin

7.1.1.10. Major protocol violations/deviations

Around 5% of the subjects in both treatment groups had at least 1 major protocol deviation. The most common major protocol deviation was intake of a wrong dose of metformin. This occurred in 5 subjects in the dapagliflozin group and 3 subjects in the placebo group.

7.1.1.11. Baseline data

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were 61 years old. The proportions of men and women were similar in both groups: around 56% men and 44% women. All patients were white and of non-Hispanic/Latino ethnicity and were from 5 European countries: 30% from Hungary, around 24% from Sweden, around 19% from the Czech Republic, around 18% from Bulgaria, and around 8% from Poland. Around two-thirds of the patients were obese (BMI ≥30 kg/m^2). The mean weight at baseline was about 91.5 kg. Around 26% of the subjects had a history of cardiovascular disease (CVD) other than hypertension.

In general, the treatment groups were balanced with respect to diabetes-related baseline characteristics. The mean duration of T2DM was 5.77 years, with 16.7% of the patients suffering from T2DM over 10 years. At baseline, the mean HbA1c was 7.17%. This mean HbA1c value was lower than for other studies in the dapagliflozin program as a consequence of the inclusion criteria, i.e., HbA1c values ≥6.5% and ≤8.5%, which were chosen to ensure that subjects continued in the trial for as long as possible without rescue to allow for BMD evaluation. Around 54% of the subjects had a baseline HbA1c between 7% and 8%, and only 7.2% of the subjects had a baseline HbA1c of at least 8%.

Mean age was somewhat higher in women (63.3 years) than in men (58.6 years). Also, the proportion of subjects of at least 65 years was larger in women (40%) than in men (25%).

These findings were anticipated considering the different age inclusion criteria for men and women. The proportion of obese subjects (BMI ≥30 kg/m^2) was larger in women (73.8%) than in men (61%). Mean body weight was greater in men (96.96 kg) than in women (84.62 kg). Mean height was greater in men (176.0 cm) than in women (160.9 cm). Mean waist circumference was greater in men (106.6 cm) than in women (103.1 cm).

7.1.1.12. Results for the efficacy outcomes

7.1.1.12.1. Bone changes at 50 weeks

· Bone mineral density

There was no change in BMD at lumbar spine (L1-4), femoral neck, and total hip in both treatment groups at week 50 (adjusted mean percent change from baseline in all anatomical regions: <0.5%). Seven patients in the dapagliflozin and 4 patients in the placebo group showed a decrease in BMD ≥5% from baseline to week 50.

· Biochemical markers of bone formation and bone resorption

Patients in the dapagliflozin group did not show a meaningful change in bone formation markers at week 50 (adjusted mean change from baseline in osteocalcin: -0.61 ng/mL, bone specific alkaline phosphatase: -0.78 U/L, and procollagen type-1 N-terminal propeptide: -1.11 µg/L), while in the placebo group a decrease of all bone formation markers was observed. The difference in the mean change of osteocalcin between dapagliflozin and placebo was statistically relevant (nominal p<0.05).

Patients in the dapagliflozin group showed an increase in C-terminal cross-linking telopeptides of type I collagen in serum (adjusted mean change from baseline: 0.04 ng/mL) and a decrease in N-terminal cross-linking telopeptides of type I collagen in urine (adjusted mean change from baseline: -41.7 nmol BCE) at week 50. Patients in the placebo group showed changes in the same direction but of smaller magnitude compared to subjects in the dapagliflozin group. The changes in the dapagliflozin group were not statistically relevant compared to the changes in the placebo group.

· Fractures

No AEs of bone fractures were noted in either treatment group.

7.1.1.12.2. Bone changes at week 102

· Bone mineral density

There was no meaningful change in BMD at lumbar spine (L1-4), femoral neck, and total hip from baseline to week 102 in the dapagliflozin group compared to the placebo group (nominal p-values for the difference in mean percent change from baseline in BMD at the 3 locations between the dapagliflozin group and the placebo group exceeded 0.05). Sixteen subjects in the dapagliflozin and placebo groups showed a decrease in BMD ≥5% from baseline to week 102 (LOCF) in any anatomical region.

· Biochemical markers of bone formation and bone resorption

Patients in the dapagliflozin and placebo groups did not show a meaningful mean change in osteocalcin, procollagen type 1 N terminal propeptide or C- and N-terminal cross linking telopeptides or type 1 collagen in serum from baseline to week 102. There was no statistically relevant difference in the mean change of any bone formation or resorption marker.

· Bone fractures

One patient in each of the dapagliflozin and placebo groups experienced an AE of bone fracture during the ST + LT periods.

7.1.1.12.3. Other Results at 102 weeks

It is important to note the amounts of missing data at the completion of the study. Subjects who discontinued from the study early resulted in missing data over the course of the study. For example, 22% of the subjects were missing total body weight observations at week 102, and the amounts of missing data were equal for both randomised treatment groups. When excluding data after rescue for total body weight, the distribution of missing data changes with 46% missing from the placebo group and 33% missing from the dapagliflozin group. Proportions in similar patterns would apply for other efficacy endpoints. This amount of missing data has unknown influence on the results and contributes to why these data are considered exploratory.

Table 3: Study D1690C00013: Summary of efficacy endpoints, including data after rescue (full analysis set)

		PLA + MET N = 91	DAPA 10MG + MET N = 89
Total body weight (kg)			
Week 24	Adjusted mean change from baseline (SE)	-1.24 (0.3126)	-3.35 (0.3194)
	Difference vs. PLA + MET (SE)		-2.12 (0.4009)
	95% CI for difference		(-2.91, -1.33)
Week 50	Adjusted mean change from baseline (SE)	-1.89 (0.3898)	-4.24 (0.3999)
	Difference vs. PLA + MET (SE)		-2.35 (0.5278)
	95% CI for difference		(-3.39, -1.31)
Week 102	Adjusted mean change from baseline (SE)	-2.12 (0.4315)	-4.54 (0.4499)
	Difference vs. PLA + MET (SE)		-2.42 (0.6167)
	95% CI for difference		(-3.64, -1.21)
Waist circumference (cm)			
Week 24	Adjusted mean change from baseline (SE)	-1.4 (0.497)	-2.9 (0.507)
	Difference vs. PLA + MET (SE)		-1.6 (0.639)
	95% CI for difference		(-2.8, -0.3)
Week 50	Adjusted mean change from baseline (SE)	-2.7 (0.628)	-4.6 (0.644)
	Difference vs. PLA + MET (SE)		-1.9 (0.852)

		PLA + MET N = 91	DAPA 10MG + MET N = 89
	95% CI for difference		(-3.6, -0.2)
Week 102	Adjusted mean change from baseline (SE)	-2.9 (0.640)	-5.0 (0.669)
	Difference vs. PLA + MET (SE)		-2.1 (0.914)
	95% CI for difference		(-3.9, -0.3)
Total body fat mass (kg)			
Week 24	Adjusted mean change from baseline (SE)	-0.65 (0.3581)	-2.16 (0.3698)
	Difference vs. PLA + MET (SE)		-1.51 (0.3680)
	95% CI for difference		(-2.24, -0.79)
Week 50	Adjusted mean change from baseline (SE)	ND	ND
	Difference vs. PLA + MET (SE)		
	95% CI for difference		
Week 102	Adjusted mean change from baseline (SE)	-1.46 (0.3985)	-2.80 (0.4403)
	Difference vs. PLA + MET (SE)		-1.34 (0.5600)
	95% CI for difference		(-2.44, -0.23)
Subjects with body weight decrease of at least 5%			
Week 24	Percent adjusted (SE)	4.3% (2.148)	27.2% (4.693)
	Difference vs. PLA + MET (SE)		22.9% (5.158)
	95% CI for difference		(12.8, 33.0)
Week 50	Percent adjusted (SE)	14.0% (3.633)	38.7% (5.116)
	Difference vs. PLA + MET (SE)		24.6% (6.239)
	95% CI for difference		(12.4, 36.9)
Week 102	Percent adjusted (SE)	16.5% (3.888)	27.1% (4.699)

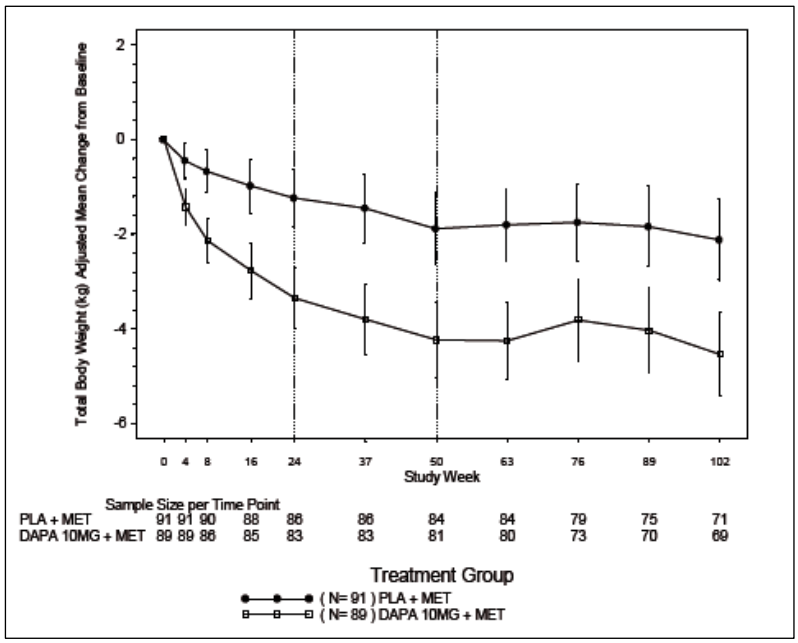
		PLA + MET N = 91	DAPA 10MG + MET N = 89
	Difference vs. PLA + MET (SE)		10.6% (6.102)
	95% CI for difference		(-1.3, 22.6)

Logistic regression based on the methodology of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu, with adjustment for baseline total body weight and stratum. In case of less than 5 events per treatment group on average, the exact method is used.

Subjects discontinued or missed measurements at the time point are considered not achieving response.

Patients in both treatment groups showed a further mean decrease in total body weight and waist circumference from week 24 to week 50 and no meaningful mean change in total body weight and waist circumference from week 50 to week 102. The mean decrease in total body weight and waist circumference from week 24 to week 50 was slightly larger in the dapagliflozin group than in the placebo group. Between week 50 and week 102 the mean decrease of total body weight and waist circumference between treatment groups remained about constant.

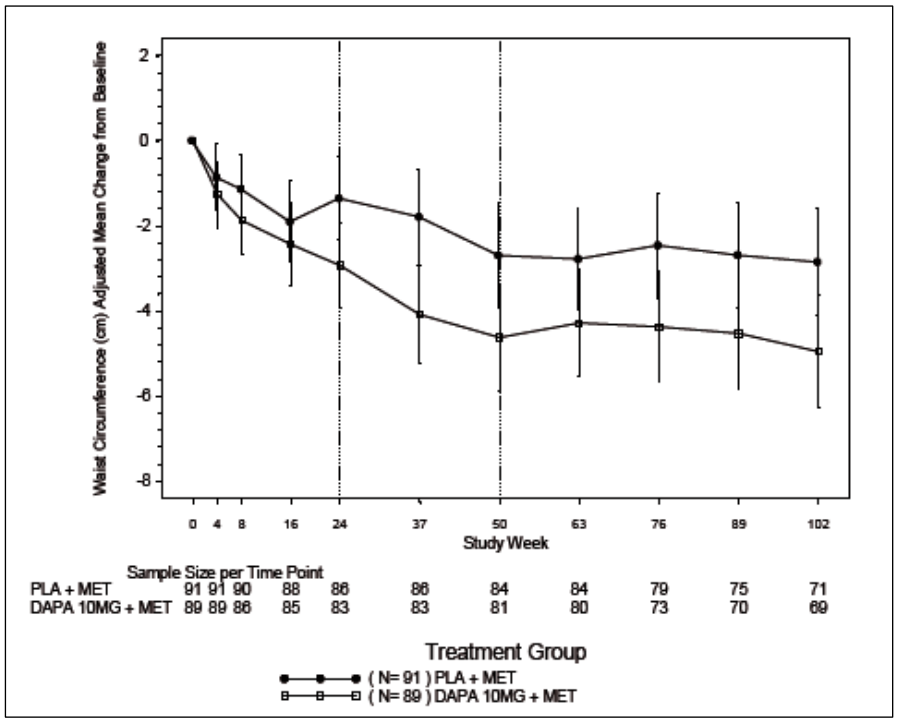
Figure 1: Study D1690C00012: Total body weight (kg) adjusted mean change from baseline over time for the ST + LT periods, including data after rescue (full analysis set)



Mean value based on repeated measures analysis model: post-baseline = baseline treatment stratum rescue week week*treatment week*baseline.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

Figure 2: Study D1690C00012: Waist circumference (cm) adjusted mean change from baseline over time for the ST + LT periods, including data after rescue (full analysis set)



Mean value based on repeated measures analysis model: post-baseline = baseline treatment stratum rescue week week*treatment week*baseline.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

Patients in both treatment groups showed a further mean decrease in total body fat mass from week 24 to week 102. The mean decrease in total body mass from week 24 to week 102 was slightly smaller in the dapagliflozin group than in the placebo group.

The proportion of patients with a decrease in total body weight of at least 5% showed a similar increase in both treatment groups from week 24 to week 50. From week 50 to week 102, the proportion of patients with a decrease in total body weight of at least 5% declined in the dapagliflozin group and remained about constant in the placebo group.

7.1.2. Summary of all pivotal efficacy studies

The studies are tabulated and summarised below.

Table 4: Summary of efficacy studies

Study No	Dapagliflozin dose	Metformin Dose	Comparator	Subject Population	Duration	Submission	Change in HBA1c (%)	Change in FPG (mmol/l)	Change in body weight (kg)
							Difference from placebo or comparator for 10 mg dose		
Drug Naïve subjects – monotherapy – morning (AM) and evening (PM) dosing									
MB102013	Gp 1: 12.5 mg, 5 mg, 10 mg QAM and QAP Gp2: 5 mg or 10 mg QAM	-	Placebo	Drug naïve patients with T2DM who have inadequate control with diet and exercise	24 weeks + 78 weeks	Original original	At 24 weeks: -0.66 At 102 weeks: -0.91	At 24 weeks: -1.4 At 102 weeks: -2.1	At 24 weeks: -0.97 At 102 weeks: -2.4
Initial combination with metformin XR (evening dosing of both dapagliflozin and metformin)									
MB10234	10 mg	Up to 2,000 mg	Dapa 10 mg Met up to 2,000 mg	Drug naïve patients with T2DM who had baseline HbA1c ≥7.5% to ≤12.0%	24 weeks	Original	-0.53 (vs dapa) -0.54 (vs met)	-0.77 (vs dapa) -1.42 (vs met)	Not tested (vs dapa) -1.97 (vs met)
MB102021	5 mg	Up to 2,000 mg	Dapa 5 mg Met up to 2,000 mg	Drug naïve patients with T2DM who had baseline HbA1c ≥7.5% to ≤12.0%	24 weeks	Original	-0.86 (vs dapa) -0.70 (vs met)	-1.1 (vs dapa) -2.0 (vs met)	No difference (vs dapa) -1.37 (vs met)
Add on combination with metformin IR									
MB102014	2.5 mg, 5 mg, 10 mg QD	≥1500 mg/day	Placebo	Patients with T2DM who have inadequate control with metformin	24 weeks + 78 weeks	Original Original	At 24 weeks: -0.54 At 102 weeks: -0.80	At 24 weeks: -1.0 At 102 weeks: -0.30	At 24 weeks: -1.97 At 102 weeks: -3.1
D1690C00012	10 mg QD	≥1500 mg/day	Placebo	Patients with T2DM who have inadequate control with metformin	24 weeks + 26 weeks + 52 weeks	Original This report This report	-0.28	Not done	-2.08 -2.3 -2.4
D1690C00004	2.5 mg, 5 mg, 10 mg	≥1500 mg/day	Glipizide titrated to 5 mg, 10 mg or 20 mg QD	Patients with T2DM who have inadequate control with metformin	52 weeks + 52 weeks	Original Original Extension	At 52 weeks: -0.00 At 104 weeks: -0.18	At 52 weeks: -0.23 At 104 weeks: -0.44	At 52 weeks: -4.65 At 104 weeks: -8.0

Table 4 continued: Summary of efficacy studies

Study No	Dapagliflozin dose	Metformin Dose	Comparator	Subject Population	Duration	Submission	Change in HBA1c (%)	Change in FPG (mmol/l)	Change in body weight (kg)
							Difference from placebo or comparator for 10 mg dose		
D1690C00010*	10 mg QD	≥1500 mg/day	Placebo Sitagliptin 100 mg/day	Patients with T2DM who have inadequate control on sitagliptin alone or in combination with metformin	24 weeks + 24 weeks	Extension Extension	At 24 weeks: -0.39 At 48 weeks: -0.59	At 24 weeks: -1.27 At 48 weeks: -1.67	At 24 weeks: -2.04 At 48 weeks: -2.07
Add on combination with insulin plus metformin IR ± maximum 2 OADs									
D1690C00006*	2.5 mg, 5 mg, 10 mg QD	Up to 2,000 mg	Placebo Insulin	Patients with T2DM who have inadequate control on insulin	24 weeks + 24 weeks + 56 weeks	Original Original Extension	At 24 weeks: -0.61 At 104 weeks: -0.65	At 24 weeks: -1.1 At 104 weeks: -0.4	At 24 weeks: -1.71 At 104 weeks: -2.88

HbA1c = haemoglobin A1c; IR = immediate release; XR = extended release; OAD = oral antidiabetic drugs, QAM = once day in the morning; QPM = once daily in the evening; QD = once daily; T2DM = type 2 diabetes mellitus
Submissions: Original (PM-2010-03812-3-5); Extension (PM-2013-01503-1-5)
* Results are for comparator +metformin alone subgroups
Source: Module 2.7.3 Table 1, 2, 12-17and amended from text, CSR and addendum tables

The following is a brief summary of these studies with comments derived from the study reports, clinical summaries and evaluation reports, as appropriate and as relevant to the fixed dose combination.

7.1.2.1. Drug Naïve subjects – monotherapy – morning (AM) and evening (PM) dosing

Study MB102013 was a multicentre, international, randomised, double blind, placebo controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin as monotherapy for T2DM inadequately controlled on diet and exercise. The trial randomised 485 patients and was conducted over 24 weeks with an extension period of 78 weeks.

The main purpose of this study in this application is to support the evening administration of the Dapagliflozin component of the FDC product.

The primary outcome measure was the change in HbA1c from baseline after 24 weeks for dapagliflozin (morning administration) versus placebo. The result was a placebo adjusted fall of 0.66% ($p<0.0001$) for the 10 mg morning administration group of 70 subjects for which the primary efficacy parameter was determined. A similar fall was observed with evening administration of dapagliflozin.

The results demonstrated that with AM administration, HbA1c fell by 0.23% in the placebo and by 0.58%, 0.77% and 0.89% in the 2.5 mg, 5 mg, and 10 mg Dapagliflozin groups respectively.

The difference from placebo 0.54% and 0.66% for the 5 mg and 10 mg groups was statistically significant ($p=0.0005$, $p<0.0001$). A statistically significant fall was also recorded in these two groups for FPG, which fell by a mean of 1.1 mmol/L and 1.4 mmol/L respectively. Body weight fell by 2-3 kg in all groups with a numerically greater reduction of 0.5 – 1 kg in the Dapagliflozin groups, but these differences did not achieve statistical significance.

With PM administration, HbA1c fell to a similar extent (0.73 – 0.86%, different from placebo (0.56 – 0.61%) in all three Dapagliflozin dosage groups.

After 99-102 weeks of treatment, HbA1c for subjects remaining in the study was lower, by comparison with baseline, than at 24 weeks, mean reduction from baseline being 0.71%, 0.91%, 1.01% and 1.15% in the placebo 2.5 mg, 5 mg and 10 mg groups respectively. The differences from placebo in the 5 mg and 10 mg groups of 0.59% and 0.45% are similar to those observed at 24 weeks but apply to only 16 and 21 subjects, respectively, remaining in follow up. The majority of subjects in this study discontinued progressively through the 102 week follow-up period due to lack of glycaemic control or need for rescue therapy. Reduction in body weight was maintained in the dapagliflozin groups irrespective of rescue, averaging 4.66 kg for 35 completing subjects at 102 weeks by comparison with 1.52 kg in placebo subjects.

The conclusion of the evaluator of the original submission was that this study provided confirmatory evidence of efficacy of dapagliflozin 5 – 10 mg as monotherapy, with maintenance of efficacy over 102 weeks only in completing patients (approximately 25% of those originally randomised).

7.1.2.2. Initial combination with metformin XR (evening dosing of both dapagliflozin and metformin)

Studies MB10234 and MB102021 were initial combination therapy studies with identical design and large numbers of patients (598 and 638 patients respectively). Dapagliflozin in combination with metformin was compared to treatment arms in which the same two medications were given alone to treatment naïve patients. Both studies were of 24 weeks duration

In Study MB10121, a 5 mg dose of dapagliflozin was used. Patients were not newly diagnosed with T2DM, but 75% had a duration of diabetes of two years or less. At 24 weeks, HbA1c had fallen by 1.19% with dapagliflozin 5 mg, 1.35% with metformin, and 2.05% with the combination therapy. The difference ("add-on" effect) of 0.86% by comparison with dapagliflozin monotherapy and 0.70% with metformin monotherapy was statistically significant

(p<0.0001). Comparable changes occurred in FPG. HbA1c <7% was achieved by 52.4% of combination therapy subjects compared with 22.5% and 34% of dapagliflozin and metformin monotherapy respectively. Combination therapy resulted on average in 1.37 kg more weight loss than with metformin alone.

In Study MB102034, the dapagliflozin dose of 10 mg proposed for marketing was used in a similar protocol and the findings were essentially the same as those in Study MB10121. With the higher dapagliflozin dose given alone, HbA1c change at 24 weeks was similar to that of metformin (-1.44%, -1.42%) and the change with the combination therapy was 2.1%, a statistically significant and clinically relevant mean difference of 0.54% compared with metformin. Similar proportion of patients in the various treatment groups achieved HbA1c <7% as in Study MB102021. Mean weight loss on combination therapy was 3.55 kg compared with 2.75 kg on dapagliflozin alone and 1.32 kg on metformin alone.

A secondary outcome of Study 102034 was demonstration that dapagliflozin 10 mg was non-inferior to metformin with respect to the HbA1c change at 24 weeks and superior (p=0.0012) in terms of reduction of FPG.

The Clinical Evaluator's conclusion was that the 10 mg had superior efficacy to the 5 mg tablet and recommended against approval of the 5 mg tablet.

7.1.2.3. Add on combination with metformin IR

Study MB102014 was a multicentre, international, randomised, double blind, placebo controlled, parallel group trial to evaluate the safety and efficacy of a range of dapagliflozin doses in combination with metformin for patients with T2DM inadequately controlled on metformin alone. The study randomised 546 patients and comprised a 24 week treatment period plus a 102 week long term extension period.

10 mg dapagliflozin produced 0.84% reduction in HbA1c compared to 0.30% with placebo, both groups continuing metformin (p-value for difference <0.0002). FPG was reduced 1.31 mmol/L compared with 0.33 mmol/L for placebo, the majority of this change being evident after one week's treatment. Weight loss was 0.89 kg with placebo and 2.86kg with 10 mg dapagliflozin. Outcomes for HbA1c and weight loss were equally satisfactory in those patients who were worst controlled and most obese at baseline. In the long term extension study which included 98% of patients (95/119 of the 10 mg dapagliflozin group) completing the 102 weeks, patients maintained 0.80% reduction in HbA1c and maintained reduction in FPG. At 102 week mean body weight change was -3.1 kg relative to placebo.

Study D1690C00012 was a body weight/body composition study, with no glycaemic endpoints and is therefore considered supportive only. It was a multicentre, international, double blind, randomised, parallel group, placebo controlled trial in which 180 patients were treated for 24 weeks and then a further 78 weeks long term extension study. The results at 24 weeks were evaluated in the original submission and the long term extension (102 weeks) was evaluated in this report (see Section 7.1.1). The patients treated with metformin were randomised to dapagliflozin 10 mg or placebo. At 24 weeks, weight loss for the 10 mg dapagliflozin group was 2.9 kg compared with 0.88 kg for placebo (p<0.0001). Waist circumference and percent body fat mass also declined in the dapagliflozin treatment group, and MRI/MRS techniques showed reduction in both abdominal subcutaneous and visceral adipose tissue.

Mean reductions in total body weight and waist circumference achieved with dapagliflozin as add-on to metformin at week 24 appeared to be accentuated until week 50 and then maintained until week 102. Also, mean reductions in total body fat mass were observed until week 102. The effect of dapagliflozin on HbA1c was maintained until week 102.

The full detailed summary of the extension study was new to this submission.

Additional support for efficacy was supplied in Study D1690C00004 which compared dapagliflozin with a sulphonylurea (glipizide) as add on treatment for T2DM patients poorly

controlled on metformin. This was an international, multicentre, randomised, parallel group trial in which 814 patients were randomised and the study consisted of 52 weeks of treatment followed by 52 weeks long term extension. The 52 week short term treatment period was evaluated in the original submission and the 52 week (total 104 week) long term extension in the extension submission.

At 52 weeks, HbA1c fell by 0.52% in both treatment groups. The decrease was statistically significantly non-inferior in the dapagliflozin group compared to glipizide. Over 104 weeks, the effect of glipizide appeared to abate after 52 weeks of treatment, whereas dapagliflozin showed more persistent glycaemic benefits (-0.32% HbA1c reduction from baseline to week 104 versus –0.14% with glipizide). The mean total body weight decrease at Week 52 (LOCF) from baseline was -3.22 kg for subjects in the dapagliflozin group, while mean total body weight increased by 1.44 kg in the glipizide group ($p < 0.0001$). Additionally, a statistically significantly higher proportion of subjects in the dapagliflozin group (33.3%), compared to the glipizide group (2.5%), reduced their body weight by ≥ 5% from baseline to Week 52 (LOCF) ($p<0.0001$). At Week 104, subjects in the dapagliflozin group still maintained a clinically relevant mean weight reduction from baseline (-3.70 kg), while subjects in the glipizide group showed a 1.36 kg increase from baseline. A clinically relevant weight loss ≥ 5% from baseline was observed in 23.8% of dapagliflozin-treated subjects versus 2.8% of glipizide-treated subjects.

Study D1690C00010 was a 24 week international, multicentre, randomised, double blind, placebo controlled, parallel group trial with a 24 week long term extension period to evaluate the safety and efficacy of dapagliflozin 10 mg daily in subjects with T2DM who have inadequate glycaemic control on a DPP-4 inhibitor (sitagliptin) alone or in combination with metformin. Patients were stratified according to their use of metformin (Stratum 2 being those patients taking metformin). A total of 452 patients were randomised, of which 228 were taking metformin. The main purpose of the study was the comparison to sitagliptin and so results are primarily presented for the total population. The placebo corrected results for Stratum 2 alone are: HbA1c -0.39% at week 24 and of -0.59% at week 48; FPG -1.27 mmol/L at week 24 and of -1.67 mmol/L at week 48; and body weight -2.04 kg at week 24 and of -2.07 kg at week 48.

7.1.2.4. Add on combination with insulin plus metformin IR ± maximum 2 OADs

Study D1690C00006 was a 24 week international, multicentre, randomised, parallel group, double blind, placebo controlled study with an 80 week extension period to evaluate the safety and efficacy of dapagliflozin therapy when added to the existing therapy of patients with T2DM with inadequate glycaemic control on insulin. A post hoc analysis was performed on the subset of patients who received dapagliflozin or placebo in combination of insulin plus metformin alone.

For the post-hoc subgroup, patients who received dapagliflozin in combination with insulin plus metformin alone, judged at a nominal two-sided alpha-level of 0.05, placebo-corrected mean reductions in HbA1c of -0.44%, -0.59% and -0.61% were achieved for dapagliflozin 2.5 mg, 5 mg and 10 mg treatment groups, respectively, which were consistent with the results of the overall population. Glycaemic efficacy was maintained until 104 weeks in all dapagliflozin treatment groups, with placebo-corrected HbA1c mean reductions of –0.88% for the dapagliflozin 5 mg/10 mg and dapagliflozin 10 mg treatment groups.

7.2. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.3. Evaluator's conclusions on clinical efficacy for treatment of T2DM

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

A two-way drug interaction study was submitted in the original application and accepted as showing no clinically meaningful effect of dapagliflozin on metformin pharmacokinetics 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 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 is acceptable as surrogate for studies in which the fixed dose combination was used.

Given the bioequivalence of the fixed dose combination tablets with the individual components there seems no reason to believe that the fixed dose combination 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 and that there was a risk of its use in patients who were at greater risk of side effects eg 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 5mg dapa/1,000 mg met). 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 morning dosing.

8. Clinical safety

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 applicant "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 dapa+met 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 dapa vs comparators rather than dapa+met vs 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 AE profile is to compare dapa+met with dapa alone and met alone or with other combinations of OADs. Only Study MB102034 compared the combination of 10 mg dapa+met 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 dapa+met vs dapa and met alone.

Studies in which the co-administration of 10mg dapa + 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.

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

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

- General adverse events (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, 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. Only symptoms and/or blood glucose values deemed by the Investigator to meet the definition of hypoglycaemia were reported and by proactively questioning the patient at each study visit for signs and symptoms of UTIs and genital infections, and when infections were reported, additional information was collected and recorded in case record form. If infection was suspected urinary culture was done.
- Laboratory tests, including standard haematology, clinical chemistry (generally AST, ALT, AP, CK, total bilirubin, BUN, electrolytes, total protein, albumin, serum creatinine, uric acid, serum cystatin C, PTH, 25 hydroxy-vitamin D, FSH, TSH) and urinalysis (glucose, blood by dipstick, albumin, creatinine), were performed at screening, baseline, and at each study visit up to 51 weeks
- ECG at baseline and at week 24 and 48
- Vital signs and physical examination at each study visit

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.3. Dose-response and non-pivotal efficacy studies

Not applicable.

8.1.4. Other studies evaluable for safety only

8.1.4.1. Clinical pharmacology studies

No new safety issues were found in in the clinical pharmacology studies.

8.1.4.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.2. Patient exposure

Table 5: 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
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 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

Table 6: 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

Studies	N	Placebo/ control	Dapa + Met	Dapa alone	Dapa + OADa
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
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 7: Duration of exposure to dapagliflozin plus metformin combination

Studies	N	Mean duration (days)		Median duration (days)		Cumulative exposure (patient years)	
		Dapa* + met	Placebo or compare	Dapa + met	Placebo or compare	Dapa+ met	Placebo or compare
MB102014	546	599.3	541.1	712.0	701.0	221.5	203.0
D1690C00012	182	612.1	642.1	714.0	714.0	152.5	160.0
D1690C00004	814	539.1	560.6	721.0	709.5	623.2	602.2
MB102034	638	154.2	155.9	168	168	NP	NP

Studies	N	Mean duration (days)		Median duration (days)		Cumulative exposure (patient years)	
		Dapa* + met	Placebo or compare	Dapa + met	Placebo or compare	Dapa+ met	Placebo or compare
MB102021	598	159.3	153.2, 154.6	168	168	NP	NP
D1690C00010 (Stratum 1)	223	308.1	306.9	337.0	337.0	93.6	94.1
D1690C00010 (Stratum 2)	228	321.3	304.6	337.0	337.0	100.3	95.1
D1690C00006	807	596.6	516.5	727	721	321.0	278.6
MB102013	485	543.1	515.9	700.0	707.0	99.6	105.9
Total	**4594**						

* dapa 10 mg strength reported when range of doses tested; met = metformin; compare = comparator

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.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

8.3.1.1.1. Study MB102034

The proportion of patients who reported at least 1 AE was slightly higher in the dapagliflozin plus metformin (59.7%) and the dapagliflozin groups (60.3%) than in the metformin (56.7%) treatment group. Hypoglycaemic events were similar in the dapagliflozin plus metformin (3.3%) and metformin (2.9%) groups compared to the dapagliflozin (0.9%) treatment groups. The 5 most common AEs at the preferred term (PT) level in descending order in the dapagliflozin 10 mg QD plus metformin group were diarrhoea, asymptomatic bacteriuria, nausea, headache and constipation.

Table 8: Study MB102034: Adverse events (≥2% in any treatment group), 24 weeks

Preferred Term	DAPA 10 mg + MET N = 211		DAPA 10 mg N = 219		MET N = 208		Total N = 638	
	No	%	No	%	No	%	No	%
Total subjects with an event	126	59.7	132	60.3	118	56.7	376	58.9
Diarrhoea	15	7.1	6	2.7	20	9.6	41	6.4
Asymptomatic bacteriuria	10	4.7	4	1.8	2	1.0	16	2.5
Nausea	10	4.7	8	3.7	5	2.4	23	3.6
Headache	9	4.3	10	4.6	5	2.4	24	3.8
Constipation	8	3.8	5	2.3	2	1.0	15	2.4
Dyslipidaemia	8	3.8	3	1.4	3	1.4	14	2.2
Pruritus genital	8	3.8	5	2.3	3	1.4	16	2.5
Cough	7	3.3	3	1.4	5	2.4	15	2.4
Dysuria	7	3.3	5	2.3	1	0.5	13	2.0
Nasopharyngitis	7	3.3	7	3.2	10	4.8	24	3.8
Upper respiratory tract infection	7	3.3	6	2.7	7	3.4	20	3.1
Vulvovaginal mycotic infection	7	3.3	11	5.0	1	0.5	19	3.0
Urinary tract infection	6	2.8	17	7.8	4	1.9	27	4.2
Abdominal pain	5	2.4	5	2.3	2	1.0	12	1.9
Back pain	5	2.4	7	3.2	6	2.9	18	2.8
Fatigue	5	2.4	2	0.9	2	1.0	9	1.4
Gastroenteritis	5	2.4	5	2.3	1	0.5	11	1.7

MedDRA Version: 13.0. N is the number of treated subjects. Included are non-serious adverse events with onset on or after the first date of double-blind treatment and on or prior to the last day of double-blind treatment plus 4 days. Included are serious adverse events with onset on or after the first date of double-blind treatment

and on or prior to the last day of double-blind treatment plus 30 days. Only hypoglycaemia reported as a serious adverse event is included.

In study MB102021, which used 5 mg dapagliflozin, the proportion of patients who reported at least 1 AE was higher in the dapagliflozin plus metformin (68.8%) group than in the dapagliflozin (52.7%) or metformin (59.2%) treatment groups. Hypoglycaemic events were higher in the dapagliflozin plus metformin (2.6%) group compared to none in the dapagliflozin and metformin monotherapy treatment groups.

The 5 most common AEs at PT level in descending order in the dapagliflozin 5 mg QD plus metformin group were diarrhoea, nausea, upper respiratory tract infection, UTI and back pain.

8.3.1.2. Other studies

8.3.1.2.1. Add-on to metformin

- Study MB102014 (dapa + met vs placebo + met)

During the 102-week treatment period, approximately 80% of the patients across all treatment groups experienced at least 1 AE. The proportion of patients experiencing at least 1 AE was similar in the dapagliflozin and placebo groups, and there was no evidence of dose dependency in the dapagliflozin groups. The proportion of subjects reporting hypoglycaemia events was also similar across the treatment groups. No major episode of hypoglycaemia was reported and no subject discontinued study treatment due to a hypoglycaemic event. The 5 most common AEs at PT level in descending order in the dapagliflozin 10 mg group were back pain, influenza, diarrhoea, UTI and headache.

- Study D1690C00012 (dapa + met vs placebo + met)

During the 102-week treatment period, the proportion of patients experiencing at least 1 AE was similar in the dapagliflozin (71.4%) and placebo groups (69.2%). Similar proportions of patients in the dapagliflozin and placebo groups experienced at least 1 hypoglycaemic event (4.4% and 5.5%, respectively). No major episode of hypoglycaemia was reported and no subject discontinued study treatment due to a hypoglycaemic event. The 5 most common AEs at PT level in descending order in the dapagliflozin 10 mg once daily (QD) group were nasopharyngitis, bone density decreased, hypertension, pneumonia and bronchitis.

8.3.1.2.2. Active comparator-glipizide

- Study D1690C00004 (dapa + met vs glipizide +met)

During the 104-week treatment period, the overall proportion of patients experiencing at least 1 AE was similar in the dapagliflozin and glipizide groups (83.0% and 82.8%, respectively. Hypoglycaemic events were reported for 4.2% of patients in the dapagliflozin group compared with 45.8% of patients in the glipizide group. The vast majority of hypoglycaemic events were classified as minor; 2.5% of patients in the dapagliflozin group and 42.4% of patients in the glipizide group reported minor episodes of hypoglycaemia. In the dapagliflozin group, no patient experienced a major hypoglycaemic event or discontinued study treatment due to a hypoglycaemic event. In the glipizide group, there were 3 (0.7%) major hypoglycaemic events and 7 (1.7%) patients discontinued study treatment due to a hypoglycaemic event. The 5 most common AEs at PT level in descending order in the dapagliflozin 10 mg QD group were nasopharyngitis, UTI, hypertension, influenza, and bronchitis.

Events suggestive of mycotic genital infections, events of UTI, and creatinine renal clearance decreased were reported in a greater proportion of subjects treated with dapagliflozin than with glipizide. AEs that occurred predominantly in the glipizide group included dizziness, arthralgia, hyperhidrosis, and tremor.

8.3.1.2.3. Add-on to other OAD – sitagliptin

· D1690C00010 (dapa + sitagliptin ± met vs placebo + sitagliptin ± met)

During the 48-week treatment period, the proportion of patients experiencing at least 1 AE was higher in the dapagliflozin group (66.2%) than in the placebo group (61.1%). Hypoglycaemic events were reported in 12 (5.3%) of patients in the dapagliflozin and 14 (6.2%) of patients in the placebo group. Most patients with a hypoglycaemic event experienced the event after rescue with glimepiride. One (1) major hypoglycaemic event was reported in 1 patient in the dapagliflozin group; this subject had not received rescue treatment. No patient discontinued study treatment due to a hypoglycaemic event. The 5 most common AEs at PT level in descending order in the dapagliflozin 10 mg group were nasopharyngitis, back pain, UTI, pharyngitis, and arthralgia.

Overall safety in Stratum 2 (sitagliptin plus metformin): The safety profile in the subgroup receiving metformin was generally consistent with the overall population, with the exception of hypoglycaemia; the proportion of patients reporting hypoglycaemic events was higher in the dapagliflozin group (5.3%) than in the placebo group (2.6%). The 5 most common AEs at PT level as ordered in the dapagliflozin 10 mg QD group were nasopharyngitis, arthralgia, back pain, UTI and diarrhoea.

8.3.1.2.4. Add-on to other OAD – insulin

· D1690C00006 (dapa + insulin ± OADs vs placebo + insulin ± OADs)

During the 104-week treatment period, around 79% of patients in all treatment groups experienced at least 1 AE. The proportion of patients experiencing at least 1 AE was similar in the dapagliflozin and placebo groups, and there was no evidence of dose dependency in the dapagliflozin groups. Overall, hypoglycaemic events were reported by approximately 63% of patients. The proportion of patients with hypoglycaemic events was slightly higher in the dapagliflozin 2.5 mg group than in the other treatment groups, including placebo. The vast majority of hypoglycaemic events were classified as minor; 66.8%, 59.0%, 59.2% and 60.4% of patients in the dapagliflozin 2.5 mg group, 5/10 mg group, 10 mg group and placebo group, respectively, reported minor episodes of hypoglycaemia. In total, 12 patients reported a major hypoglycaemic event, and these were evenly distributed across all treatment groups, including placebo; 2.0%, 1.4%, 1.5% and 1.0% of subjects in the dapagliflozin 2.5 mg group, 5/10 mg group, 10 mg group and placebo group, respectively, reported major episodes of hypoglycaemia. No patient discontinued study treatment due to a hypoglycaemic event. The 5 most common AEs at PT level in descending order in the dapagliflozin 10 mg QD group were nasopharyngitis, hypertension, UTI, back pain and arthralgia.

Overall safety in the subgroup receiving metformin: The safety profile in the subgroup receiving metformin was generally consistent with the overall population. While the total proportion of patients experiencing at least 1 AE was higher in the subgroup (84.2%) compared with the overall population (79.2%), the proportions remained balanced across treatment groups. The 5 most common AEs at PT level, as ordered in the dapagliflozin 10 mg QD group, were nasopharyngitis, hypertension, pain in extremity, arthralgia, and diarrhoea.

8.3.2. Treatment-related adverse events (adverse drug reactions)

The treatment related AEs are not discussed in detail in the study reports or Summaries.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

Data on deaths is given for the entire dapagliflozin development program, including studies not included in this application. The following table provides the total information provided in the Summaries.

Table 9: Deaths during the dapagliflozin development program

Categories	Placebo/control N = 3184	DAPA + MET N = 2488	DAPA - MET N = 3013
Deaths	18 (0.6)	10 (0.4)	19 (0.6)

N = number of treated subjects

Data in the Table above includes all Phase 2b and 3 Pool includes studies MB102008, MB102009, MB102013, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, MB102045, D1690C00004, D1692C00005, D1690C00005, D1690C00006, D1690C00010, D1690C00012, D1690C00018 and D1690C00019; but does not include 1 mg treatment group from Studies MB102032 and D1692C00005.

DAPA + MET group = subjects who took dapagliflozin added to metformin (IR or XR) in Studies MB102014, MB102021, MB102034, MB102045, D1690C00004, D1690C00012, and subgroups of MB102009, MB102035, D1690C00006, D1690C00010, D1690C00018 and D1690C00019.

DAPA - MET group = subjects who took dapagliflozin as monotherapy or added to other anti-diabetic therapies.

8.3.3.2. Other SAEs

8.3.3.2.1. Pivotal studies

- Study MB102034

SAEs were reported for few patients, with similar proportions of subjects (1.4% to 2.3%) reported in all of the treatment groups. SAEs of overdose were reported in 2 patients in the metformin group. All other SAEs were reported by 1 patient in any treatment group.

- Study MB102021

Few SAEs were reported, with similar proportions of patients (3.15 to 4.4%) reported in all treatment groups. SAEs of pulmonary tuberculosis were reported in 3 patients in the dapagliflozin plus metformin group. SAEs of diabetes mellitus were reported in 2 patients in the dapagliflozin group. All other SAEs were reported by 1 subject in any treatment group.

8.3.3.2.2. Other studies

- Add-on to metformin
  - Study MB102014 (dapa + met vs placebo + met):

    Similar proportions of subjects in the dapagliflozin and placebo groups reported an SAE (6.6% to 10.9% in the dapagliflozin groups and 10.2% in the placebo group). SAEs of chest pain were reported in 2 patients in the dapagliflozin 10 mg group, SAEs of myocardial infarction were reported in 2 patients in the dapagliflozin 2.5 mg group, and SAEs of acute myocardial infarction and cardiac arrest were reported in 3 and 2 patients, respectively, in the placebo group. All other SAEs were reported by 1 patient in any treatment group.
  - Study D1690C00012 (dapa + met vs placebo + met):

    The proportion of subjects reporting SAEs was similar in the dapagliflozin group and placebo group (17.6% and 15.4%, respectively). SAEs of pneumonia were reported in 3 patients in the dapagliflozin group and 1 patient in the placebo group. All other SAEs were reported by ≤ 2 patients in either treatment group.
- Active comparator-glipizide

- Study D1690C00004 (dapa + met vs glipizide +met)

  Instances of SAEs were slightly higher in the glipizide group than in the dapagliflozin group (15.2% and 12.6%, respectively). SAEs of myocardial infarction, diverticulitis, hypoglycaemia and anaemia were each reported in 3 patients in the glipizide group and SAEs of prostate cancer were reported in 3 patients in the dapagliflozin group. All other SAEs were reported by ≤ 2 patients in either treatment group.

· Add-on to other OAD – sitagliptin

- D1690C00010 (dapa + sitagliptin ± met vs placebo + sitagliptin ± met)

  Similar proportions of subjects in the dapagliflozin and placebo groups reported an SAE (6.7% in the dapagliflozin group and 8.0% in the placebo group. SAEs of basal cell carcinoma were reported in 3 patients in the placebo group and SAEs of chronic obstructive pulmonary disease and abdominal pain upper were each reported in 2 patients in the dapagliflozin group. All other SAEs were reported by 1 patient in any treatment group.

  SAEs in Stratum 2 (sitagliptin plus metformin): The safety profile in the subgroup receiving metformin was consistent with the overall population. The proportion of subjects with an SAE was similar across treatment groups (11.4% in the placebo group and 10.5% in the dapagliflozin group).

· Add-on to other OAD –insulin

- D1690C00006 (dapa + insulin ± OADs vs placebo + insulin ± OADs)

  Similar proportions of subjects in the dapagliflozin and placebo groups reported an SAE (15.1% to 19.3% in the dapagliflozin groups and 19.8% in the placebo group. SAEs of transient ischaemic attack were reported in 3 patients in the placebo group and SAEs of osteoarthritis were reported in 3 patients in the dapagliflozin 2.5 mg group. All other SAEs were reported by ≤ 2 patients in any treatment group.

  SAEs in the subgroup receiving metformin: The safety profile in the subgroup receiving metformin was consistent with the overall population. The proportion of patients with an SAE was similar across all treatment groups (23.8% in the placebo group and 12.5% to 19.0% in the dapagliflozin groups.

8.3.4. Discontinuation due to adverse events

Across the studies included in the Summary of Clinical Safety, no consistent pattern in premature discontinuation of study medication due to AEs was observed that would suggest any specific safety concerns for dapagliflozin in combination with metformin.

The overall pattern of discontinuations observed in the studies included in the Summary of Clinical Safety was generally consistent with that previously reported for the pooled safety datasets in the initial dapagliflozin dossier. In the placebo-controlled pool in the initial dapagliflozin dossier, the most commonly reported premature discontinuation of study medication due to an AE across all dapagliflozin treatment groups (N = 3291) were as follows:

· Blood creatinine increased: 8 subjects (0.2%) versus 2 subjects (0.1%) in placebo (N = 1393). (In several of the studies there were protocol specified discontinuation criteria for blood creatinine).

· Urinary tract infection: 6 subjects (0.2%) versus 0 subjects in placebo

· Nausea: 5 subjects (0.2%) versus 1 subject (0.1%) in placebo

· Dizziness: 4 subjects (0.1%) versus 0 subjects in placebo

· Fatigue: 3 subjects (0.1%) versus 2 subjects (0.1%) in placebo

In subjects treated with dapagliflozin 10 mg (N = 1193), the most commonly reported events leading to discontinuation were increased blood creatinine (0.4%), UTIs (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%) (Forxiga PI).

8.3.4.1. Pivotal studies

8.3.4.1.1. Study MB102034

Few subjects reported AEs that led to premature discontinuation of treatment: the proportion was lower in the dapagliflozin plus metformin group (1.9%) than in the dapagliflozin (4.1%) or metformin (3.8%) monotherapy treatment groups. No AE (preferred term) led to the discontinuation of more than 1 dapagliflozin-treated subject.

8.3.4.1.2. Study MB102021

Few patients reported AEs that led to premature discontinuation of treatment; the proportion was lower in the dapagliflozin plus metformin group (1.0%) than in the dapagliflozin (2.5%) or metformin (3.0%) monotherapy treatment groups. AEs that led to the discontinuation of more than 1 dapagliflozin-treated subject were pulmonary tuberculosis (2 subjects in the dapagliflozin plus metformin group and 1 subject in the dapagliflozin and metformin groups, respectively).

8.3.4.2. Other studies

8.3.4.2.1. Add-on to metformin

- Study MB102014 (dapa + met vs placebo + met)

Similar proportions of patients in the dapagliflozin and placebo groups discontinued study medication due to an AE (3.6% to 5.1% in the dapagliflozin groups and 6.6% in the placebo group). AEs that led to the discontinuation of more than 1 dapagliflozin-treated patient were blood creatinine increased (2 patients in the dapagliflozin 2.5 mg group, 1 patient each in the dapagliflozin 5 and 10 mg groups, and 1 patient in the placebo group) and renal failure (2 patients in the dapagliflozin 5 mg group, and no patients in the other dapagliflozin groups and the placebo group). AEs of blood creatinine increased were reported due to study-specific discontinuation criteria regarding blood creatinine, which was also instructed to be reported as an AE. These events were also reported as renal impairment or failures.

- Study D1690C00012 (dapa + met vs placebo + met)

More patients discontinued study medication due to an AE in the dapagliflozin group than in the placebo group (15.4% and 4.4%, respectively). AEs that led to the discontinuation of more than 1 dapagliflozin-treated patient were: bone density decreased (5 patients in the dapagliflozin group and 4 patient in the placebo group) and blood creatinine increased (5 patients in the dapagliflozin group and 4 patients in the placebo group).

8.3.4.2.2. Active comparator-glipizide

- Study D1690C00004 (dapa + met vs glipizide +met)

More patients discontinued study medication due to an AE in the dapagliflozin group than in the glipizide group (9.9% and 7.6%, respectively). AEs that led to the discontinuation of more than 1 dapagliflozin-treated patient and more than 1 glipizide-treated patient were: creatinine renal clearance decreased (13 patients in the dapagliflozin group and 8 patients in the glipizide group); renal impairment (3 and 4 patients, respectively); prostate cancer (2 patients in the dapagliflozin group and no patients in the glipizide group); balanitis (2 and 0 patients, respectively). AEs that led to the discontinuation of more than 1 glipizide-treated subject were diarrhoea (3 patients in the glipizide group and no patients in the dapagliflozin group), myocardial infarction (2 and 0 patients, respectively), and anaemia (2 and 0 patients, respectively).

8.3.4.2.3. Add-on to other OAD – sitagliptin

· D1690C00010 (dapa + sitagliptin ± met vs placebo + sitagliptin ± met)

Similar proportions of subjects in the dapagliflozin and placebo groups discontinued study medication due to an AE [3.1% in each group]). No AE led to the discontinuation in more than one dapagliflozin treated patient. The AE that led to the discontinuation of more than 1 placebo-treated subject was renal impairment (2 patients in the placebo group and 1 patient in the dapagliflozin group).

AEs leading to discontinuation of study therapy in Stratum 2 (sitagliptin plus metformin): The safety profile in the subgroup receiving metformin was consistent with the overall population. AEs leading to discontinuation of study therapy were reported by similar proportions of patients across treatment groups (3.5% in the dapagliflozin group and 5.3% in the placebo group.

8.3.4.2.4. Add-on to other OAD –insulin

· D1690C00006 (dapa + insulin ± OADs vs placebo + insulin ± OADs)

Similar proportions of subjects in the dapagliflozin and placebo groups discontinued study medication due to an AE [5.0% to 9.4% in the dapagliflozin groups and 6.6% in the placebo group])

AEs that led to the discontinuation of more than 1 dapagliflozin-treated patient were blood creatinine increased (3, 2 and 1 patients in the dapagliflozin 10 mg, 5/10 mg, and 2.5 mg groups, respectively, and no patients in the placebo group) and UTI (2 patients in the dapagliflozin 5/10 mg group and no patients in any of the other treatment groups). AEs of blood creatinine increased were reported due to study-specific discontinuation In addition, creatinine clearance and blood creatinine were also to be reported as AEs. These events were also reported as renal impairment or failures.

AEs leading to premature discontinuation of treatment of study therapy in the subgroup receiving metformin: The safety profile in the subgroup receiving metformin was consistent with the overall population. AEs leading to discontinuation of study therapy were reported by similar proportions of patients across treatment groups (0% to 8.9% in the dapagliflozin groups and 6.3% in the placebo group).

8.3.5. Adverse events of special interest

8.3.5.1. Hypoglycaemia

Due to its insulin independent mechanism of action and its dependence on the filtered load of glucose, dapagliflozin has a low intrinsic risk of hypoglycaemia. However, the most frequently reported AE in the dapagliflozin Product Information (PI) is hypoglycaemia, mostly based on the background therapy used in each study.

Review of the total AE database included in this submission, the combination of dapagliflozin and metformin as long term therapy was not associated with an increased propensity to develop hypoglycaemia. The safety findings in these individual studies were generally consistent with those reported in the initial dapagliflozin dossier. For studies of dapagliflozin in combination with metformin alone, or with sitagliptin, the frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo (< 5% up to 102 weeks; < 4% up to 24 weeks). Higher rates of hypoglycaemia were observed in the combination study with insulin or sulphonylurea. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo.

8.3.5.2. Volume depletion

Due to its mechanism of action, dapagliflozin increases diuresis, leading to a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose

concentrations. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted. The Diabex XR PI notes that special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with non-steroidal anti-inflammatory drugs.

No new safety signal relating to volume depletion was observed with dapagliflozin as add-on to metformin or in the long term extension to the efficacy studies included in this submission.

8.3.5.3. Genital infections

Genital infections are recognised in the prescribing information as occurring more frequently with dapagliflozin than with comparators. In the review of all AEs reported in the clinical studies submitted in this submission the increased rate of infections was observed, as previously reported. The proportions of patients with events of genital infections were 8.2% for dapagliflozin 10 mg and 1.3% for placebo. Of the patients treated with dapagliflozin 10 mg who experienced an infection, 74.6% had only one and 15.8% had 3 or more infections. Of the patients treated with placebo who experienced an infection, 77.8% had only one and none had 3 or more infections (Forxiga PI).

No new safety signal regarding genital infections was observed with dapagliflozin as add-on to metformin in the long-term extensions of the efficacy studies included in this submission.

8.3.5.4. Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of UTI as recognised in the dapagliflozin PI. No new safety signal regarding UTI was observed with dapagliflozin as add-on to metformin or in the LT extensions of the efficacy studies included in this submission, and there were no imbalances observed regarding kidney infections.

8.3.5.5. Neoplasms

The current dapagliflozin PI recognises bladder cancer, breast cancer and prostate cancer as potential risks of dapagliflozin due to imbalances for these cancer types in the efficacy clinical trials, though the imbalances were not statistically significant.

No new cases of breast and bladder cancer were observed in the 8 efficacy studies included in this submission since the analysis for the previous submission. Two (2) new events of prostate cancer were reported in Study D1690C00004 (during the 104-week long-term extension period); 1 event in the dapagliflozin treatment group and 1 post-study event in the comparator treatment group. The reported cancer events occurred across the clinical programme and in different treatment combinations, suggesting no increased risk when dapagliflozin is combined with metformin specifically.

8.3.5.6. Bone fracture

Bone fracture was identified as a potential risk based on mean increases in markers of bone resorption in dapagliflozin treated subjects compared with placebo treated subjects observed in the early dapagliflozin clinical studies.

No new bone related safety signal was observed following treatment with dapagliflozin add on to metformin or in the long term extension to the efficacy studies.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

8.4.1.1.1. Study MB102034

During the 24-week clinical study period, no clinically relevant changes from baseline were seen in liver function tests for any treatment group.

8.4.1.1.2. Study MB102021

During the 24-week clinical study period, no clinically relevant changes from baseline were seen in liver function tests for any treatment group.

8.4.1.2. Other studies

8.4.1.2.1. Add-on to metformin

· Study MB102014

During the 102-week treatment period, no clinically relevant changes from baseline were seen in liver function tests for any treatment group.

· Study D1690C00012

During the 102-week treatment period, patients in the dapagliflozin and placebo group showed a slight decrease in mean AST and ALT. A slight mean decrease in mean ALP and TBL was observed in the placebo group only.

8.4.1.2.2. Active comparator-glipizide

· Study D1690C00004

During the 104-week treatment period, patients in the dapagliflozin group showed a slight decrease in mean ALT and no clinically relevant changes in mean AST, ALP and TBL from baseline to Week 104. Patients in the glipizide group showed no clinically relevant changes in mean ALT, AST, ALP and TBL from baseline to Week 104.

8.4.1.2.3. Add-on to other OAD – sitagliptin

· D1690C00010

During the 48-week ST + LT period, patients in the dapagliflozin group showed a decrease in mean AST and ALT from baseline to Week 12 with no further change to Week 48 and no clinically relevant changes in mean ALP and TBL to Week 48. Subjects in the placebo group showed no clinically relevant changes in mean AST, ALT, ALP and TBL from baseline to Week 48.

8.4.1.2.4. Add-on to other OAD –insulin

· D1690C00006

During the 104-week ST + LT1 + LT2 period, patients in the dapagliflozin groups showed a slight decrease in mean ALT and no clinically relevant changes in mean AST, ALP and TBL from baseline to Week 104. Subjects in the placebo group showed no clinically relevant changes in mean AST, ALT, ALP and TBL from baseline to Week 104.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

8.4.2.1.1. Study MB102034

No clinically relevant changes from baseline were seen for any treatment group in mean serum creatinine concentration, mean calculated creatinine clearance or eGFR.

8.4.2.1.2. Study MB102021

No clinically relevant changes from baseline were seen for any treatment group in mean serum creatinine concentration or mean calculated creatinine clearance. Mean increases from baseline in eGFR were observed in all treatment groups at Week 24, with a larger increase in the metformin and dapagliflozin plus metformin groups than in the dapagliflozin group.

8.4.2.2. Other studies

8.4.2.2.1. Add-on to metformin

· Study MB102014

No clinically relevant changes from baseline were seen for any treatment group in mean serum creatinine concentration or mean calculated creatinine clearance. Increases from baseline in eGFR were consistently observed in all treatment groups beginning at Week 24. At Week 102, the mean increases were larger in the dapagliflozin 5 mg and 10 mg groups than in the placebo and dapagliflozin 2.5 mg group.

· Study D1690C00012

No clinically relevant changes from baseline were seen for any treatment group in mean serum creatinine concentration. A slight decrease in mean calculated creatinine clearance was observed from baseline to Week 102 in both treatment groups. No clinically relevant mean changes from baseline in mean eGFR: were seen for either treatment group.

8.4.2.2.2. Active comparator-glipizide

· Study D1690C00004

Patients in the dapagliflozin group showed no clinically relevant changes from baseline to Week 52 in mean serum creatinine concentration. Patients in the glipizide group showed a slight increase from baseline to Week 52. Patients in the dapagliflozin group showed a decrease from baseline to Week 26 in mean calculated creatinine clearance that remained stable thereafter. Patients in the glipizide group showed a decrease at Week 26 that grew larger until Week 104, but the decrease was still more pronounced in the dapagliflozin group. Patients in the dapagliflozin group showed no clinically relevant changes from baseline to Week 104 in mean eGFR. Patients in the glipizide group showed a decrease from baseline to Week 26 that remained stable thereafter.

8.4.2.2.3. Add-on to other OAD – sitagliptin

· D1690C00010

No clinically relevant changes from baseline were seen for any treatment group in mean serum creatinine concentration, mean calculated creatinine clearance or eGFR.

8.4.2.2.4. Add-on to other OAD – insulin

· D1690C00006

No clinically relevant changes from baseline were seen for any treatment group in mean serum creatinine concentration or mean calculated creatinine clearance. Patients in the dapagliflozin groups showed a slight decrease from baseline to Week 48 in eGFR followed by a gradual increase to baseline level in the dapagliflozin 5/10 mg group but not in the other dapagliflozin

groups. At follow-up, most of the changes observed at Week 104 in the dapagliflozin 2.5 and 10 mg groups were reversible in the safety analysis set as well as in all subjects completing the study.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

8.4.3.1.1. Study MB102034

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, bicarbonate, magnesium and inorganic phosphorus were observed from baseline to Week 24 in any treatment group. A higher proportions of patients in the dapagliflozin plus metformin and dapagliflozin treatment groups (7 and 13 subjects, respectively) had marked abnormalities (MAs) of inorganic phosphorus compared with the metformin treatment group (3 subjects). All these MAs were reversible and isolated events. Four (4) patients (1 patient in the dapagliflozin plus metformin treatment group, 2 patients in the dapagliflozin treatment group, and 1 patient in the metformin treatment group) had isolated and reversible MAs of serum calcium concentrations < 7.5 mg/dL.

8.4.3.1.2. Study MB102021

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, bicarbonate, magnesium and inorganic phosphorus were observed from baseline to Week 24 in any treatment group.

8.4.3.2. Other studies

8.4.3.2.1. Add-on to metformin

· Study MB102014

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, bicarbonate, magnesium and inorganic phosphorus were observed from baseline to Week 102 in any treatment group. Few marked abnormalities of serum electrolytes including calcium and inorganic phosphorus were observed and were equally distributed between the dapagliflozin groups and the placebo group.

· Study D1690C00012

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, and bicarbonate were observed from baseline to Week 102 in any treatment group. Patients in the dapagliflozin group showed a reversible increase in mean inorganic phosphorus from baseline to Week 102; the clinical relevance of these increases is not known. Few MAs of serum electrolytes including calcium and inorganic phosphorus were observed and were equally distributed between the dapagliflozin group and the placebo group.

8.4.3.2.2. Active comparator-glipizide

· Study D1690C00004

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, and bicarbonate were observed from baseline to Week 104 in any treatment group. patients in the dapagliflozin group showed a slight increase in magnesium and inorganic phosphorus from baseline to Week 3; magnesium returned to baseline levels by Week 104 while inorganic phosphorus showed a further slight increase between Week 78 and Week 104. Patients in the glipizide group showed no meaningful mean change in magnesium until Week 52 followed by a gradual decrease until Week 104, and a slight increase in inorganic phosphorus from baseline to Week 3 with a further slight increase between Week 78 and Week 104. The clinical relevance of these increases is not known. Few MAs of serum electrolytes

including calcium and inorganic phosphorus were observed and were equally distributed between the treatment groups.

8.4.3.2.3. Add-on to other OAD – sitagliptin

· D1690C00010

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, bicarbonate, and inorganic phosphorus were observed from baseline to Week 48 in any treatment group. Patients in the dapagliflozin group showed an increase in magnesium from baseline to Week 4, which remained stable through Week 48. Few MAs of serum electrolytes including calcium and inorganic phosphorus were observed and were equally distributed between the treatment groups.

8.4.3.2.4. Add-on to insulin

· D1690C00006

Overall, no clinically relevant changes in mean values of serum protein, albumin, sodium, potassium, calcium, chloride, and bicarbonate were observed from baseline to Week 104 in any treatment group. Patients in the dapagliflozin groups showed a slight increase in magnesium and inorganic phosphorus from baseline to Week 24, which generally abated between Week 24 and Week 104; the clinical relevance of these increases is not known. The proportion of patients with calcium concentration < 1.87 mmol/L was higher in the dapagliflozin groups (6 to 8 patients) compared with placebo (2 patients). One (1) patient in the dapagliflozin 2.5 mg group and 2 patients in the dapagliflozin 10 mg group showed serum calcium concentrations ≥0.25 mmol/L from ULN and ≥0.12 mmol/L from baseline. None of these patients reported an AE associated with hypocalcaemia.

8.4.4. Haematology

Small but consistent increases in haematocrit were observed among dapagliflozin treated patients across the entire dapagliflozin clinical programme, which are likely related to the mild plasma volume depletion associated with the diuretic effect of dapagliflozin. With dapagliflozin monotherapy mean haematocrit increases from baseline were observed (2.15% for dapagliflozin 10 mg versus -0.40% for placebo). Overall, changes in haematological parameters were generally small, consistent across the programme, either normalised or trended toward normalisation after dapagliflozin discontinuation, and were not associated with an increase in potentially related AEs.

8.4.4.1. Pivotal studies

8.4.4.1.1. Study MB102034

The frequency of haematocrit values > 55% were reported in 0.5%, 1.8% and 0.5% of patients in the dapagliflozin plus metformin, dapagliflozin and metformin groups, respectively. Haemoglobin concentration > 180 g/L was reported in 2.4%, 1.8% and 10.5% of patients in the dapagliflozin plus metformin, dapagliflozin and metformin groups, respectively. No patients reported associated thromboembolic AEs. No patient had a haematocrit > 60% or a haemoglobin concentration > 200 g/L.

8.4.4.1.2. Study MB102021

The frequency of haematocrit values > 55% were reported in 1.6%, 0.5% and 0.5% of patients in the dapagliflozin plus metformin, dapagliflozin and metformin groups, respectively. Haemoglobin concentration > 180 g/L was reported in 0.5%, 1.0% and 0.5% of patients in the dapagliflozin plus metformin, dapagliflozin and metformin groups, respectively. No patients reported associated thromboembolic AEs. No patient had haematocrit > 60% or haemoglobin concentration > 200 g/L.

8.4.4.2. Other studies

8.4.4.2.1. Add-on to metformin

· Study MB102014

The frequency of haematocrit values > 55% was reported in 1.5% to 2.3% of subjects treated with dapagliflozin and in 0.7% of patients in the placebo group. Haemoglobin concentration > 180 g/L was reported in 0.7% to 3.8% of patients treated with dapagliflozin and in 0.7% of subjects in the placebo group. No patients reported haematocrit > 60% or haemoglobin > 200 g/L. In all patients, the abnormalities were transient and resolved without intervention. No patients reported associated thromboembolic AEs. Patients in the dapagliflozin groups showed a dose-dependent mean increase in haemoglobin and haematocrit from baseline to Week 12, which remained stable thereafter until Week 102, while mean decreases were observed in the placebo group up to Week 102.

· Study D1690C00012

The frequency of haematocrit values > 55% were reported in 1.1% of patients each in the dapagliflozin group and placebo group. Haemoglobin concentration > 180 g/L was reported in 2.3% of patients in the dapagliflozin group and in 1.1% of patients in the placebo group. No patients reported associated thromboembolic AEs. No patient in either treatment group had haematocrit > 60% or haemoglobin concentration > 200 g/L. Patients in the dapagliflozin group (but not the placebo group) showed a slight increase in mean haemoglobin, haematocrit, and red blood cell count.

8.4.4.2.2. Active comparator-glipizide

· Study D1690C00004

The frequency of haematocrit values > 55% were reported in 1.3% of patients in the dapagliflozin group and no patient in the glipizide group. Haemoglobin concentration > 180 g/L was reported in 1% of patient in the dapagliflozin group and in 0.3% of patient in the glipizide group. No patient reported associated thromboembolic AEs. Haematocrit > 60% was reported in 0.3% of patients in the dapagliflozin group, but no haemoglobin concentration > 200 g/L was observed. Patients in the dapagliflozin group showed a mean increase in haemoglobin, haematocrit, and red blood cell count from baseline to Week 26, which remained stable thereafter until Week 104, while no patients in the glipizide group showed any meaningful mean change up to Week 104.

8.4.4.2.3. Add-on to other OAD – sitagliptin

· D1690C00010

The frequency of haematocrit values > 55% were reported in 4.5% of patients in the dapagliflozin group and in 0.4% of patients in the placebo group. Haemoglobin concentration > 180 g/L was reported in 3.1% of patients in the dapagliflozin group and in 1 patient (0.4%) in the placebo group. Haematocrit values > 60% were reported in 1 patient (0.4%) in the dapagliflozin group and no patients in the placebo group. No patients reported haemoglobin concentration > 200 g/L. No patients reported associated thromboembolic AEs. Patients in the dapagliflozin group showed a slight increase in mean haemoglobin, haematocrit, and red blood cell count from baseline to Week 12, which remained stable thereafter until Week 48, while no mean changes were observed in the placebo group up to Week 48.

8.4.4.2.4. Add-on to insulin

· D1690C00006

The frequency of haematocrit values > 55% were reported in 1.5% to 5.5% of subjects in the dapagliflozin groups (with the highest proportion in the dapagliflozin 10 mg QPM group) and no

patients in the placebo group. One (1) patient in the dapagliflozin 10 mg group showed a single haematocrit of 60.4%. Haemoglobin concentration > 18 g/dL (> 180 g/L) was reported in 1.5% to 8.2% of patients in the dapagliflozin groups (with the highest proportion in the dapagliflozin 10 mg QPM group) and in 0.5% of patients in the placebo group. No patients reported haemoglobin concentration > 200 g/L. One (1) patient in the dapagliflozin 5/10 mg group, who had multiple risk factors for atherosclerosis/hypercoagulable state, had an AE of peripheral arterial occlusive disease and was later hospitalised for a thromboarterectomy. This patient also had an elevated haematocrit level at baseline (54%) and an elevated haematocrit (55%) during the study. Patients in the dapagliflozin groups showed a dose-dependent mean increase in haemoglobin, haematocrit and red blood cell count from baseline to Week 12, which remained almost stable thereafter until Week 104, while no mean changes were observed in the placebo group up to Week 104. At follow-up, the increase in haematocrit was partially reversed.

8.4.5. Electrocardiograph

ECG assessments did not change from baseline to later time points across all treatment groups in the efficacy studies included in this submission. The majority of patients with normal ECG tracings at baseline also had normal tracings at later time points. Proportions of patients with a change in ECG assessment from normal to abnormal did not show a meaningful difference between treatment groups. Only 2 patients across all the trials included in this submission, both in the dapagliflozin 2.5 mg treatment group of Study MB102014, reported serious rhythm distributions (serious atrial fibrillation and serious second degree atrioventricular block, which were both assessed by the investigator as not related to study medication). Across the studies included in this submission, ECG-measured heart rate, QRS duration, PR interval, QT interval, and unspecified QT interval corrected for heart rate using a study-specific factor (QTc) did not show any clinically meaningful mean changes from baseline to end of treatment in any treatment groups.

8.4.6. Vital signs

No safety signals or trends were identified for dapagliflozin from vital signs or physical findings.

8.4.7. Blood pressure

Slight mean reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed during the initial short-term treatment periods in dapagliflozin-treated patients in the efficacy studies included in this submission. Proportions of patients with orthostatic hypotension (fall in SBP of > 20 mmHg or DBP of > 10 mmHg [supine to standing]) during the full treatment periods were consistent across all treatment groups, including placebo. Results from the efficacy studies included in this submission indicate that dapagliflozin in combination with metformin does not appreciably increase the risk of AEs associated with lowering of blood pressure such as hypotension, orthostatic hypotension, hypovolaemia, and electrolyte abnormalities.

8.5. Post-marketing experience

Not applicable as product is not marketed in any country.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Renal impairment

Renal impairment/failure is identified as a potential risk in the 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 ≥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. 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 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 (CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m^2).

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.

8.6.2. Liver toxicity

Liver injury is included as a potential risk in the RMP due to one subject in Study D1690C00004[2] 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 ALT or AST > 3 x ULN with concomitant or subsequent TBL ≥2 x ULN was reported in ≤ 0.2% of patients treated with dapagliflozin or control. All of these patients had co-morbidities that could explain these events.

The dapa/met 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.

8.6.3. 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.

8.7. Other safety issues

8.7.1. Safety in special populations

No studies were conducted using the dapa/met XR FDC.

8.7.2. 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 dapa/met XR FDC.

[2] Identified in original submission and included in PI

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

8.8. Evaluator's overall conclusions on clinical 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.

9. First round benefit-risk assessment

9.1. 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 oral antidiabetic drugs
- 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

9.2. 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

9.3. First round assessment of benefit-risk balance

The benefit risk balance is not favourable for the dapagliflozin 5 mg combination ie dapa/met 5/1,000 mg.

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

10. First round recommendation regarding authorisation

The 5 mg/1,000 mg strength should be rejected on the basis of no additional data was submitted addressing the issues relating to the reasons for its rejection in the initial application ie, 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 PI.

11. Clinical questions

11.1. Product Information

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 D1690C000010) 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 5mg/1,000 mg combination tablet should be removed
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.
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 tablet; further justification should be provided.

12. Second round evaluation of clinical data submitted in response to questions

[AusPAR note: The following evaluation of sponsor's responses to TGA question was prepared by the Delegate]

12.1. 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.

12.1.1. Sponsor's response:

The Sponsor considers the proposed indication is appropriate for use of the fixed dose combination 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* etc) allows for the safe and efficacious use of the fixed dose combination.

12.1.2. TGA evaluation of response:

The EMA INDICATION for XIGDUO (dapaglipflozin 5mg/metformin 850mg) 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.*

12.2. 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.

12.2.1. 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).

12.2.2. TGA evaluation of sponsor response:

The response is acceptable.

12.3. Question 3

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

12.3.1. 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 of no additional data was submitted addressing the issues relating to the reasons for its rejection in the initial application i.e., insufficient efficacy for the 5mg 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 (i.e. 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 10mg 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 Product Information), 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 5mg/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 fixed dose combination with a free form extended release metformin tablet to achieve a 2,000 mg metformin dose. Additionally, when administered in this manner, the fixed dose combination 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 5mg /1,000 mg presentation to be appropriate when used in accordance with the dosing recommendation in the proposed PI.

12.3.2. TGA evaluation of sponsor's response

A 2000mg dose of metformin could be obtained by combining the 10mg/1000mg tablet with a 1000mg tablet of metformin. The DOSAGE & ADMINISTRATION section would need to be edited to reflect this.

12.4. 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.

12.4.1. 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.

12.4.2. TGA evaluation of sponsor's response:

The response is acceptable.

12.5. 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.

12.5.1. 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 fixed dose combination products.

12.5.2. TGA evaluation of sponsor response:

The response is acceptable.

[Additional TGA and sponsor comments on the draft PI are not included in this CER Extract.]

13. Second round benefit-risk assessment

Not required.

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