Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dapagliflozin propanediol monohydrate

Proprietary Product Name: Appebb, AZ Dapagliflozin, BMS Dapagliflozin, BMS/AZ Dapagliflozin, Edistride, Empliciti and Forxiga

Sponsor: Bristol-Myers Squibb Australia Pty Ltd / AstraZeneca Pty Ltd

January 2013

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 Ageing, and is responsible for regulating medicines and medical devices.
- 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 <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	5 October 2012
Active ingredient(s):	Dapagliflozin propanediol monohydrate
Product Name(s):	Appebb, AZ Dapagliflozin, BMS Dapagliflozin, BMS/AZ Dapagliflozin, Edistride, Empliciti and Forxiga
Sponsor's Name	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Court, Mulgrave ,VIC 3170
Dose form(s):	Film-coated tablets
Strength(s):	10 mg
Container(s):	Aluminium (Al)/Al blister
Pack size(s):	7 and 28 tablets
Approved Therapeutic use:	"Monotherapy Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated. Initial combination Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels). Add-on combination Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated in patients with type 2 diabetes mellitus to improve glycemic control:

	· in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycemic control; · in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycemic control; · in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control."
Route(s) of administration:	Oral
Dosage:	Abridged: The recommended dose of Forxiga is 10 mg taken once daily at any time of the day regardless of meals. Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga should not be used in patients with moderate to severe renal impairment (eGFR<60 mL/min/1.73m^2 by MDRD or CrCl <60 mL/min by Cockcroft –Gault) No dosage adjustment for Forxiga is necessary for patients with mild or moderate hepatic impairment. Forxiga should not be used in patients with severe hepatic impairment.
ARTG Number (s)	180139, 180146, 180141, 180149, 180150, 180152 and 180147

Product background

This AusPAR describes the application by Bristol-Myers Squibb to register a new chemical entity, dapagliflozin, for use in the treatment of diabetes.

Dapagliflozin is the first of a new class of drugs. It is a selective and reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2), which is selectively expressed in the kidney. SGLT2 is the major transporter for glucose reabsorption in the kidney. The inhibition of renal glucose reabsorption results in glucose excretion in the urine, producing a feature of poorly controlled diabetes mellitus, glycosuria.

Dapagliflozin shares some of the biological properties of phlorizin, a plant flavonoid originally isolated from the bark of the apple tree by French chemists in the 19th century.[1] Phlorizin inhibits sodium-dependent glucose co transporter type 1 (SGLT1), which is primarily responsible for intestinal glucose absorption as well as SGLT2.

The development of dapagliflozin as a functional analogue of phlorizin whose action is specific to the renal tubular variant of SGLT thus has support in concept as a novel therapy independent of insulin action. A potential benefit of this approach may be freedom from some of the disadvantages of those diabetes therapies which increase the secretion or enhance the action of insulin, such as hypoglycaemia and weight gain.

The sponsor has proposed the following indications:

"Monotherapy

[1] Analyse des Phloridzins. Petersen C. Annales Academie Science Francaise 15: 178 (1835)

Indicated as an adjunct to diet and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance."

Add-on combination

Initial combination

Indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with Type 2 diabetes mellitus when dual dapagliflozin and metformin therapy is appropriate.

Add-on combination:

Indicated in patients with Type 2 diabetes mellitus to improve glycemic control in combination with metformin, a thiazolidinedione (TZD), a sulfonylurea (SU), or insulin (alone or with up to two oral anti-diabetic medications) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

The proposed dose is 10 mg once daily.

Regulatory status

The following table provides a list of major countries in which a similar application has been submitted and/or approved and the status of these applications.

Table 1. International regulatory status

Submission and approval status Country	Submission date	Status	Comment
European Union	December 2010	Under evaluation	CHMP opinion expected 19 April 2012
United States	December 2010	Under evaluation	Complete Response Letter received January 2012
Canada	January 2011	Under evaluation	Notice of Noncompliance obtained in January with response due in April 2012
Switzerland	February 2011	Under evaluation	Responded to first round of questions in October 2011
Brazil	February 2011	Not approved	File rejected in October 2011, resubmission being discussed with HA
Chile	March 2011	Under evaluation	No significant comments to date
South Africa	March 2011	Under evaluation	No significant comments to date
New Zealand	May 2011	Under evaluation	Questions received in November 2011, responses in progress and due March 2012
Ukraine	May 2011	Under evaluation`	No significant comments to date

Submission and approval status Country	Submission date	Status	Comment
Russia	June 2011	Under evaluation	No significant comments to date
Mexico	October 2011	Under evaluation	No significant comments to date

CHMP=Committee for Medicinal Products for Human Use

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

List of abbreviations used in this AusPAR

AE	adverse event
AGI	alpha glucosidase inhibitor
ANCOVA	analysis of covariance
BMI	body mass index
BMS	Bristol-Myers Squibb
CI	confidence interval
CrCl	creatinine clearance
CYP450	cytochrome P-450 enzyme system
CV	coefficient of variation
DEXA	dual energy x-ray absorptiometry
DPP	dipeptidyl peptidase
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Evaluation Agency
FPG	fasting plasma glucose
GFR	glomerular filtration rate
HCTZ	hydrochlorothiazide
IVRS	interactive voice response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LC-MS-MS	liquid chromatography with tandem mass spectrometry
MA	marked abnormality
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NCI	National Cancer Institute
PPK	population pharmacokinetics

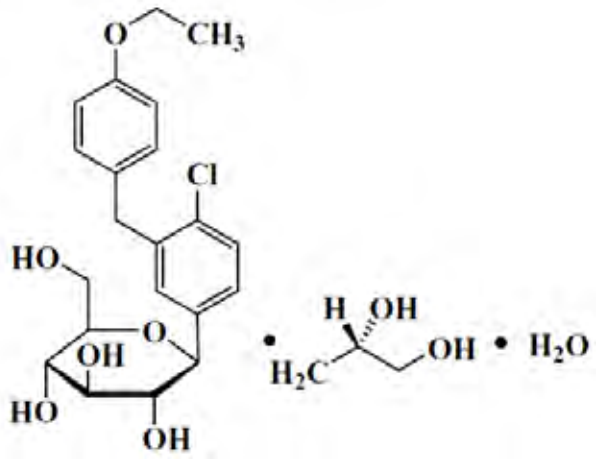
PTH	parathyroid hormone
SAE	severe adverse event
SD	standard deviation
SGLT	sodium-glucose co transporter
SEER	Surveillance, Epidemiology and End Results (NCI program)
SOC	system organ class
SU	sulphonylurea
Tm	tubular maximum for reabsorption
TZD	thiazolidinedione
ULN	upper limit of normal
ULOQ	upper limit of quantification
UGT	uridine diphosphate glucuronosyltransferase

II. Quality findings

Drug substance (active ingredient)

Dapagliflozin is a synthetic aryl glycoside. It has multiple chiral centres but the drug is a single enantiomer. Epimerisation is unlikely.

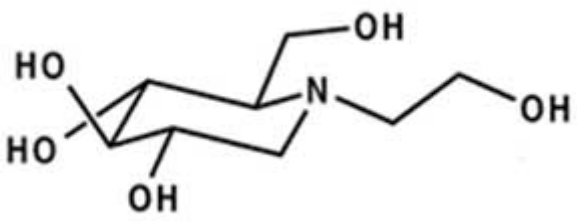
Figure 1. Chemical structure of dapagliflozin



dapagliflozin (propylene glycol, monohydrate solvate)

The structure is not closely related to that of other antidiabetic drugs; it perhaps bears some similarity to miglitol (Figure 2).

Figure 2. Chemical structure of miglitol.



The drug substance used in tablet manufacture is the 1,2-propanediol, monohydrate solvate of dapagliflozin (1,2-propanediol is also known as propylene glycol).

The drug substance is crystalline. Dapagliflozin aqueous solubility is relatively high and independent of pH.

Drug product

The proposed 5 mg and 10 mg (as dapagliflozin) tablets are, immediate release, film coated tablets with conventional formulations. Both strengths are yellow; they are distinguished by size, shape (5 mg round; 10 mg diamond) and tablet markings ('5' and '1427'; *vs* '10' and '1428'). Neither is scored.

Some clinical trials also used 2.5 mg tablets.

The Phase III clinical trial formulation differed from the proposed formulation but no impact on bioavailability is expected.

The tablets are packed in aluminium/aluminium blisters in 7 or 28 tablet packs. Supportive dissolution and disintegration data are available from the proposed manufacturing sites. The proposal was considered acceptable.

Levels of impurities in dapagliflozin tablet batches are low although the proposed limits are lax. Limited on-going related substance testing will be done via an annual program testing stability of a batch. The approach was considered acceptable.

Tablet stability data otherwise support the proposed shelf life of 24 months when stored below 30°C.

Biopharmaceutics

Three bioavailability studies were reviewed.

Study MB102059 measured absolute bioavailability. This used a radioactive carbon (^{14}C) labelled dapagliflozin intravenous (IV) dose given almost simultaneously with an oral 10 mg tablet dose. The mean absolute bioavailability was 78%.

Study MB102019 was the definitive food effect study (10 mg tablet). In 14 healthy male and female subjects, a high fat meal decreased peak plasma concentration (C_{max}) of dapagliflozin and its 3-O-glucuronide metabolite by 31% and 43%, respectively (and delayed T_{max} by about 1 h) but did not significantly alter the extent of absorption.

Studies MB102062 and MB 102090 investigated the bioequivalence of heat-stressed tablets and showed equivalence.

An acceptable justification has been provided in relation to the absence of bioequivalence data for the 5 mg strength.

Advisory committee considerations

Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM)

This application was considered at the 140th meeting of the PSC:

- The use of a tablet disintegration test in place of a tablet dissolution test was considered acceptable if supported by sufficient batch data. Sufficient data have been provided.

- The sponsor's proposal of not testing related substances at release was considered to require undertakings about future confirmatory testing. This is now considered acceptable.
- If the drug product is manufactured at more than one manufacturing site, the PSC stated that process validation, batch analysis and stability data should be provided on the drug product manufactured at each of these sites. Adequate data and assurances have been provided with regard to batch data and validation data. Given that the registration of a new tablet manufacturing site after registration does not need submission of stability data, this will not be pursued. (Stability data are routinely generated for all sites as part of Good Manufacturing Practice.) Thus, the evaluator recommended registration of both sites.

In relation to the PI, the PSC recommended that the pharmacometric analysis should be formally reviewed and the PI amended to make it clear that the relevant data were derived from a population pharmacokinetic analysis.

The PSC otherwise considered that there should be no objection to registration on pharmaceutic and biopharmaceutic grounds.

Quality summary and conclusions

Registration was recommended with respect to chemistry and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was high, with all pivotal studies conducted under Good Laboratory Practice (GLP) conditions. No major deficiencies were identified.

Pharmacology

Primary pharmacology

The sodium-glucose transporter (SGLT) family is composed of seven members (SGLT1, SGLT2. SGLT3, SGLT4, SGLT5, SGLT6, SMIT1). Quantitative reverse transcription polymerase chain reaction (RT-PCR), northern blot analysis and *in situ* hybridisation studies demonstrated that SGLT1 is expressed in the small intestine and kidney of both rats and humans while SGLT2 is expressed almost exclusively in the kidneys. The other SGLT isoforms were also expressed in the kidney and small intestine, with one isoform expressed in the central nervous system (CNS). In normal healthy individuals, glucose in plasma is filtered by the kidneys but nearly all is reabsorbed by SGLT2 with <1% excreted in urine.[2] The other SGLT isoforms are thought to have only a minor role if any, in renal glucose reabsorption.[2,3] Inhibition of SGLT2 by dapagliflozin is envisaged to reduce the level of reabsorption and promote excretion of excess glucose in the urine, thereby lowering plasma glucose levels.

[2] Zhao, F.-Q. And A.F. Keating. (2007) Functional properties and genomics of glucose transporters. *Current Genomics* **8:** 113–128.

[3] Wright, E.M., D.D.F. Loo and B.A. Hirayama. (2011) Biology of human sodium glucose transporters. *Physiol. Rev.* **91:** 733–794.

When tested in *in vitro* assays with recombinantly expressed human transporters, dapagliflozin was a competitive reversible inhibitor of SGLT2 with a K_i[4] of 0.2 nM and an 50% inhibitory concentration (IC_{50}) of 1.2 nM, at least 25 times lower than the estimated maximum clinical free plasma concentration (30 nM[5]) at the 10 mg dose. Dapagliflozin was also shown to be an inhibitor of SGLT1 but with a K_i of 610 nM and an IC_{50} of at least 1100 nM (that is,~900–3000-times less potent than at SGLT2). These concentrations are more than 20 times the maximum clinical free plasma concentration at the 10 mg dose and thus inhibition of systemic SGLT1 is not expected to occur clinically. Local concentrations in the gastrointestinal tract, where SGLT1 is also expressed, will be much higher though (~98 μM, based on a 10 mg tablet in 250 mL liquid). The major human metabolite dapagliflozin 3-O-glucuronide was not an inhibitor of SGLT1 or SGLT2 at clinically relevant concentrations and is therefore not expected to contribute to the pharmacological activity. Desethyl dapagliflozin, a metabolite in animal species, was shown to be equipotent for SGLT2 inhibition and contribute ~19% efficacy in glucose excretion in rats. However, this metabolite was not prominent in humans.

Dapagliflozin had similar potency against the mouse, rat, dog and human SGLT2 isoforms. However, in the laboratory animal species there was less selectivity for this transporter over SGLT1 (130, 207 and 436 times in the respective species compared to ≥917 times in humans).

The *in vivo* efficacy of dapagliflozin was assessed in wild-type mice and rats, and in rat models of Type 1 and Type 2 diabetes. Decreased plasma glucose with increased urinary output and urinary glucose excretion were consistently seen following single oral administration. The 50% effective concentration (ED_{50}) for a plasma glucose lowering effect over 24 h in diabetic rats (ZDF, model for Type 2 diabetes) was ~1 mg/kg orally (PO) (area under the plasma concentration effect curve from 0 to 6 h (AUC_{0-6h}) ~5229 nM·h [= 2138 ng·h/mL]; ~5 times the clinical AUC_{0-24h}). This dose was shown to completely inhibit glucose reabsorption in wild-type normoglycaemic rats. The plasma glucose lowering ability of dapagliflozin was apparent at lower doses in diabetic rats (≥0.03 mg/kg PO and ≥0.1 mg/kg PO in rat models of Type 1 and Type 2 diabetes, respectively), than in normoglycaemic ones (≥1 mg/kg PO). The dapagliflozin exposure ($AUC_{0-6h\ of}$ 1147 nM.h [= 469 ng·h/mL]) at doses resulting in a significant reduction in blood glucose levels in ZDF diabetic rats (Type 2 diabetes) was approximately equivalent to the clinical AUC_{0-24h}. Hypoglycaemia was not observed in any of the studies and dapagliflozin had no acute effect on insulin levels.

Repeated administration of dapagliflozin to diabetic ZDF rats (≥0.01 mg/kg PO for 14 days) reduced fasting glucose levels with no effect on fasting plasma insulin levels. Urine glucose excretion was not significantly different in the fed state but a trend to increased glucose excretion was observed in the fasted state. The ED_{50} was 0.03–0.06 mg/kg PO for subchronic fasting plasma glucose lowering and 0.45 mg/kg PO for fed plasma glucose lowering (AUC_{0-6h} estimated to be ~2348 nM·h [= 960 ng·h/mL]; ~2 times the clinical AUC_{0-24h}).

Hyperinsulinaemic euglycaemic clamp studies in diabetic rats indicated 0.5 mg/kg/day PO dapagliflozin for 14 days enhanced insulin sensitivity. With 5 weeks of once daily dapagliflozin treatment, fasting pancreatic insulin content was significantly increased at this dose and an improvement in pancreatic islet morphology index was seen at 1 mg/kg/day PO, suggesting an improvement in β-cell number or insulin content of β cells or both. Treatment for 5 weeks (0.5 mg/kg/day PO) to diabetic rats prevented the progressive rise in glycated haemoglobin (HbA_{1C}) and prevented the development of hyperglycaemia (at 1 mg/kg/day PO). Taken together, these findings suggest dapagliflozin

[4] K_i=equilibrium dissociation constant of a ligand
[5] Based on a C_{max} of 136 ng/mL, a free plasma fraction of 9% and a molecular mass of 409.

may delay the progression of Type 2 diabetes mellitus. Weight loss was observed in dietary induced obese rats treated with 1 mg/kg/day PO dapagliflozin for 25 days and given a restricted diet. An increase in ketone body formation indicated a change to a catabolic state. Body composition was altered in these rats with a decrease in body fat and an increase in lean mass.

Secondary pharmacodynamics

At concentrations up to 100 μM (3333 times the maximum clinical free plasma concentration), no significant inhibition of the human facilitative glucose transporters GLUT1, GLUT2 and GLUT4 was observed. No significant inhibition was observed with dapagliflozin at concentrations up to 10 μM or more (~333 times the maximum clinical free plasma concentration) in a broader screen against 40 different receptors, enzymes and ion channels. In similar screens, the major human metabolite dapagliflozin 3-O-glucuronide and the animal-specific metabolite desethyl dapagliflozin had no significant inhibitory activity up to 10 and 30 μM, respectively. Therefore, no off-target activities are predicted at the proposed clinical dose.

Safety pharmacology

Specialised safety pharmacology studies covered the cardiovascular system, while potential effects on the CNS, respiratory and renal systems were examined in toxicity studies. *In vitro*, dapagliflozin (30 μM) inhibited the hERG potassium (K^+) tail current (15%); however only minimal effects (3% inhibition) were seen at 10 μM (333 times the maximum clinical free plasma concentration). No effect on action potential duration were seen in experiments with rabbit Purkinje fibres (≤30 μM), and no consistent effects on the QT interval[6] were seen in dogs treated with ≤250 mg/kg/day PO dapagliflozin (C_{max} 176 μg/mL; animal:human exposure ratio based on C_{max} [ER_{Cmax}] ~1290). Based on large safety margins, no adverse cardiovascular effects are predicted at the proposed clinical dose.

In toxicity studies, there were no clinical signs of CNS toxicity in mice, rats or dogs (ER_{Cmax}, 581 in mice, 691 in rats and 1294 in dogs). No abnormalities were identified in neuroelectrophysiological examinations in rats treated with ≤150 mg/kg/day for 6 months or ≤200 mg/kg/day for 3 months (ER_{AUC}, >2300) or dogs with ≤120 mg/kg/day for 12 months or ≤180 mg/kg/day for 3 months (ER_{AUC}, >3300). In a 1 month study dedicated to examining neurotoxicity in mice there were no microscopic changes in the central or peripheral nervous systems at doses ≤300 mg/kg/day PO (ER_{AUC} estimated to be at least 1300[7]). Therefore, there are no particular CNS concerns predicted at the proposed dose level.

No drug-related effects on respiratory function was seen in mice at ≤400 mg/kg/day PO, in rats at ≤200 mg/kg/day PO or dogs at ≤250 mg/kg/day PO. Peak plasma levels at these doses are estimated to be 581, 691 and 1294 times the clinical C_{max} in mice, rats and dogs, respectively.

As expected based on its pharmacology, dapagliflozin induced glucosuria and osmotic diuresis at all doses tested (≥5 mg/kg/day PO) in the various repeat-dose toxicity studies, conducted in mice, rats and dogs. Hypercalciuria and natriuresis were also seen. The

[6] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

[7] Based on data in Study DN04088.

increased excretion of electrolytes is considered secondary to the pharmacological action of dapagliflozin and is consistent with an osmotic diuretic effect.[8]

Pharmacokinetics

Dapagliflozin was rapidly absorbed by the oral route in all species studied (mice, rats, dogs, Cynomolgus monkeys and human subjects) with time to peak plasma concentration (T_{max}) values ranging from 0.5–1.9 h. Although dapagliflozin was found to be a substrate of P-glycoprotein, this is unlikely to affect absorption as dapagliflozin had high intrinsic permeability, comparable to compounds that exhibit good absorption. Oral bioavailability was high in rats, dogs and humans (78–84%) but lower in Cynomolgus monkeys (25%). There were no sex differences in dapagliflozin exposure in rats, dogs or human subjects but female mice consistently had higher exposures than their male counterparts. The lower dapagliflozin exposures in male mice correlated with higher desethyl dapagliflozin exposures, suggesting a greater rate of metabolism in male mice *cf* females. The plasma half-life of dapagliflozin was moderate in rats, dogs and Cynomolgus monkeys (3.5–7.4 h) but longer in human subjects (13 h). There was no evidence of accumulation with repeat daily dosing. The volume of distribution was similar to total body water in dogs and Cynomolgus monkeys (0.8 L/kg) and greater than total body water in rats and humans (1.4–1.6 L/kg). Clearance was roughly similar in rats and Cynomolgus monkeys (4.8 –6.4 mL/min/kg), but slightly slower in humans (2.5 mL/min/kg) and dogs (1.5 mL/min/kg).

The active metabolite desethyl dapagliflozin was detected in the plasma of the laboratory animal species (0.1–1.7% of dapagliflozin exposures) but was not detected in human plasma. Dapagliflozin 3-O-glucuronide was only a minor metabolite in mice, rats and dogs, with exposures (based on plasma AUC) only 3.4%, 0.36% and 5.3%, respectively, that for dapagliflozin. In comparison, the exposure to this metabolite in human subjects was significantly greater than exposures to the parent drug (183% at the clinical dose). While this metabolite is not pharmacologically active, the much higher levels in human plasma compared to animal plasma will be considered during safety assessments.

Protein binding by dapagliflozin and the main human metabolite, dapagliflozin 3-O-glucuronide, was high (89–95%) and independent of concentration in mouse rat, dog, rabbit and human plasma. Some distribution (37%) into red blood cells was seen. Following oral administration of radioactive carbon (^{14}C) labelled dapagliflozin, radioactivity was widely distributed in rats. Aside from organs involved in excretion, significant radioactivity was seen in the adrenals, pancreas, Harderian gland and salivary gland. There was no significant penetration of the blood-brain barrier and no specific binding to melanin. The kidney showed peak and overall levels of exposure to radioactivity ~ 3–5 times higher than for blood.

Metabolism of dapagliflozin involved dealkylation, oxidation (at various sites) and glucuronidation. The latter pathway was more prominent in human subjects than in the laboratory animal species (mice, rats and dogs). At least 17 metabolites were detected across species and matrices. Dapagliflozin was the main drug related material in the plasma of animals, while for human plasma, dapagliflozin and dapagliflozin 3-O-glucuronide were the dominant forms. The latter metabolite was also by far the predominant component of drug related material in human urine. With the exception of desethyl dapagliflozin 3-O-glucuronide, all metabolites identified in human plasma were also observed in the plasma of at least one of the animal species. This metabolite, however, was detected in the excreta of all animal species examined. *In vitro* experiments revealed a

[8] Jackson, E.K. (1996) Diuretics. *In:* Molinoff, P.B. and R.W. Ruddon, ed. Goodman and Gillman, The pharmacological basis of therapeutics. New York: McGraw-Hill; 9th edition. P 685–714.

low rate of dapagliflozin metabolism in liver microsomes and hepatocytes from mice, rats, dogs and humans. Dapagliflozin 3-O-glucuronide was identified in mouse, rat, dog and human hepatocyte incubations. However, the production of this metabolite in humans is likely predominantly due to glucuronidation in the kidneys. No data were provided to indicate that glucuronidation of dapagliflozin occurs in the kidneys of animals. *In vitro* studies with recombinant human UDP-glucuronosyltransferase (UGT) enzymes indicated a major role for the extra-hepatically expressed isoform, UGT1A9, in the production of dapagliflozin 3-O-glucuronide. Some variability in dapagliflozin exposure may be seen in patients containing one of a number of naturally-occurring polymorphisms of the UGT1A9 gene (or flanking region) which affects the activity or expression level of this enzyme.[9] The liver enzymes, UGT2B4 and UGT2B7 are likely involved in the formation of another minor glucuronide, dapagliflozin 2-O-glucuronide. Cytochrome P450 isozyme CYP1A1 was the major CYP isoform involved in the oxidative metabolism of dapagliflozin, although this pathway is not a prominent degradative pathway in humans.

Drug related material was excreted roughly equally in the urine and faeces in rodents, while excretion was predominantly in the faeces in dogs and urine in humans. The higher urinary excretion in humans correlated with the higher levels of dapagliflozin 3-O-glucuronide. Given the extensive role of the kidney in the clearance of dapagliflozin, greater dapagliflozin exposure may be seen in patients with renal impairment.

Aside from the higher levels of dapagliflozin 3-O-glucuronide, the pharmacokinetic profile of dapagliflozin was qualitatively similar in humans and the species used in toxicity studies (mice, rats and dogs) and they are considered adequate to serve as appropriate models for toxicity.

Pharmacokinetic drug interactions

UGT1A9 is the major enzyme involved in dapagliflozin metabolism and it is possible that inhibitors of this isozyme could alter the exposure of dapagliflozin clinically. No significant inhibition of human CYPs (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) or transporters (P-glycoprotein, hOCT2, hOAT1 or hOAT3) was seen at clinically-relevant dapagliflozin concentrations (IC_{50} ≥33 mM; 99 times the clinical C_{max} for total drug). No significant induction of CYP1A2, 2B6 or 3A4 isoforms (messenger ribonucleic acid (mRNA) or activity) was seen in cultures of human hepatocytes at concentrations up to 20 mM (ER_{Cmax}, 60). Dapagliflozin 3-O-glucuronide was a substrate of hOAT3 (K_m, 115 mM) but was not an inhibitor of the renal transporters, hOCT2, hOAT1 or hOAT3, at clinically relevant concentrations (IC_{50} values, ≥100 mM).

Dapagliflozin is proposed to be used as monotherapy or in conjunction with various other currently approved anti-diabetic therapies. No nonclinical studies were submitted to examine the effect of dapagliflozin on the pharmacokinetics of co-administered drugs; however, based on the findings above, dapagliflozin is not expected to alter the pharmacokinetics of co-administered drugs. Inhibitors of UGT1A9 may affect the plasma kinetics of dapagliflozin.

[9] Girard, H., M.H. Court, O. Bernard, L.C. Fortier, L. Villeneuve, Q. Hao *et al.* (2004) Identification of common polymorphisms in the promoter of the UGT1A9 gene: evidence that UGT1A9 protein and activity levels are strongly genetically controlled in the liver. *Pharmacogenetics* **14:** 501–515.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice and rats using animals of both sexes and in female dogs. The clinical route (PO) was used in all studies together with an observation period of 14 days in accordance with the TGA adopted EU guideline for single dose toxicity.[10] All doses tested would be expected to generate plasma concentrations vastly in excess of that attained clinically. Gross pathological analyses were only conducted in the rodent studies. The maximum non lethal dose of dapagliflozin by the oral route was 1500 mg/kg and 375 mg/kg in mice and rats and the highest tested dose in dogs, 1000 mg/kg (at least 340 times the clinical dose on a body surface area basis), suggesting a low order of toxicity by the oral route. Clinical signs of toxicity included hypoactivity and hunched posture in mice and rats (at ≥750 mg/kg PO), while emesis was seen in dogs at ≥200 mg/kg PO. A transient decrease in body weight gain or body weight loss was seen in mice at 3000 mg/kg PO and in rats at ≥375 mg/kg PO. No target organs for toxicity were identified.

Repeat dose toxicity

Studies by the oral route of up to 3 months duration were conducted in mice, 6 months in rats and 12 months in dogs. The duration of the pivotal studies, the species used, group sizes and the use of both sexes were consistent with TGA adopted EU guidelines.[11] Dose selection in the pivotal studies was appropriate. Target organs for toxicity were the urinary system, adrenals and bones in rats, with vascular mineralisation observed in multiple organs. No consistent target organs were identified in mice or dogs.

Relative exposure

Relative exposure levels achieved in repeat dose toxicity studies have been calculated as the ratio of the plasma AUC for dapagliflozin in animals (average AUC across all tested time points) to that of humans at the recommended dose (10 mg/day) (Table 2). Very high relative exposures to dapagliflozin were achieved in the repeat dose toxicity studies. As dapagliflozin 3-O-glucuronide is a major metabolite in humans (with exposure levels greater than the parent), cross-species exposure comparisons were made for this metabolite. Dapagliflozin 3-O-glucuronide levels were not measured in repeat dose toxicity studies but were in single dose toxicity studies in rats and dogs. Calculations made below are based on these data, with $AUC_{0\text{-}24h}$ values for this metabolite being 0.36% and 5.3%, that of dapagliflozin in the respective species. Dapagliflozin 3-O-glucuronide exposures were 3.4% those of dapagliflozin in a mouse single dose study with radiolabelled dapagliflozin. Only male mice were examined but the extent of glucuronidation is assumed to be similar in females as it is in the other species. Exposures to dapagliflozin 3-O-glucuronide in mice and rats were up to 45 and 6 times, respectively, the clinical exposure in repeat dose toxicity studies but only 1.4 and 0.3 times, respectively, the clinical exposure in the carcinogenicity studies. Exposures to dapagliflozin 3-O-glucuronide achieved in the dog studies are estimated to be at least several times the clinical exposure and very large multiples at the upper dose levels.

[10] 3BS1a Single Dose Toxicity. http://www.tga.gov.au/pdf/euguide/vol3bs1aen.pdf
[11] CPMP/SWP/1042/99 Rev 1 .Guideline on repeated dose toxicity. http://www.tga.gov.au/pdf/euguide/swp104209enrev1.pdf

Table 2. Relative exposure to dapagliflozin and its major metabolite in selected repeat-dose toxicity studies. Table continued across three pages.

Species (strain)	Study	Treatment duration		Dose (mg/kg/day) PO	Dapagliflozin		Dapagliflozin 3-O-glucuronide	
					AUC0–24 h (µg·h/mL)	Exposure ratio	AUC0–24 h (µg·h/mL)	Exposure ratio
Mouse (CD-1)	DN06024	1 week		4.1 (♂/♀)	2.1 / 8.5	5 / 19	0.071 / 0.29	0.1 / 0.4
				25 (♂/♀)	17 / 46	39 / 105	0.58 / 1.56	0.7 / 1.9
				43 (♂/♀)	47 / 113	107 / 258	1.60 / 3.84	2.0 / 5
				75 (♂/♀)	96 / 298	219 / 680	3.26 / 10.1	4 / 13
	DN04088	3 months		50 (♂/♀)	44 / 121	100 / 276	1.50 / 4.1	1.9 / 5
				150 (♂/♀)	304 / 492	694 / 1123	10.3 / 16.7	13 / 21
				250 (♂/♀)	497 / 1060	1135 / 2420	16.9 / 36.0	21 / 45
	DN6072 [carc.]	2 years		2 (♀)	5.1	12	0.17	0.2
				5 (♂)	2.0	5	0.068	0.08
				10 (♀)	24	55	0.82	1.0
				15 (♂)	6.4	15	0.22	0.27
				20 (♀)	49	112	1.67	2.1
				40 (♂)	34	78	1.16	1.4
Rat (SD)	DN03049	1 month		5	21.6	49	0.078	0.1
				50	282	644	1.02	1.3
				300	1326	3027	4.77	6
	DN09009 [juvenile]	2 mths	21 days old	1 (♂/♀)	9.9 / 12	23 / 27	–	–
				15 (♂/♀)	167 / 176	381 / 402	–	–
				75 (♂/♀)	849 / 937	1938 / 2139	–	–
			83 days old	1 (♂/♀)	7 / 9.6	16 / 22	–	–
				15 (♂/♀)	97 / 135	221 / 308	–	–

Species (strain)	Study	Treatment duration	Dose (mg/kg/day) PO	Dapagliflozin		Dapagliflozin 3-O-glucuronide	
				AUC0–24 h (µg·h/mL)	Exposure ratio	AUC0–24 h (µg·h/mL)	Exposure ratio
			75 (♂/♀)	505 / 779	1153 / 1779	–	–
	DN04043	3 months	5	46	105	0.17	0.2
			50	357	816	1.29	1.6
			200	1135	2591	4.1	5
	DN05030 [pivotal]	6 months	5	40	91	0.143	0.2
			25	200	457	0.72	0.9
			150	1024	2337	3.7	5
	DN01103	6 months	15	99	226	0.36	0.4
			75	409	935	1.47	1.8
			150	844	1927	3.04	4
	DN06073 [carc.]	2 years	0.5	3.6	8	0.013	0.02
			2	14	32	0.050	0.06
			10	74	169	0.266	0.33
Dog (Beagle)	DN03050	1 month	5	62	142	3.3	4
			25	351	800	19	23
			250	2265	5172	120	150
	DN04041	3 months	5	70	159	3.7	5
			30	560	1277	30	37
			180	2258	5154	120	149
	DN05031 [pivotal]	12 months	5	52	118	2.7	3.4
			20	230	525	12.2	15
			120	1265	2888	67	83

Species (strain)	Study	Treatment duration	Dose (mg/kg/day) PO	Dapagliflozin		Dapagliflozin 3-O-glucuronide	
				AUC0–24 h (µg·h/mL)	Exposure ratio	AUC0–24 h (µg·h/mL)	Exposure ratio
Human	MB102027	Single dose	10 mg	0.438	–	0.803	–

Effect on food and water consumption and body weight changes

Treatment with dapagliflozin increased water consumption and urine output at all doses tested in rats and dogs. These parameters were not assessed in the mouse toxicity studies but earlier pharmacology studies support increased urine output at all doses tested in mice as well. Increased food consumption was also seen in mice and rats at all tested doses (food was available *ad libitum*[12] in the rodent studies). Increased food consumption was also noted in the pivotal dog study at all doses (with food provided as a daily ration). No effect on food consumption was evident in the other dog studies but given that a smaller ration of food was offered and controls ate most or virtually all of it, hyperphagia in the treated groups may not have been able to be demonstrated. Increased food and water consumption and increased urinary output are consistent with observations in SGLT2-knockout animals.[13, 14] Clinical or serum chemistry signs of dehydration were not observed in the toxicity studies, suggesting the increased fluid intake was adequate to compensate for the urinary loss. Animals had free access to water in these studies.

In pharmacology studies in which diabetic (ZDF) rats received 10 mg/kg dapagliflozin PO (ER_{AUC}, ~50), azotaemia in association with decreased food and water intake, increased urine output and increased serum concentrations of protein, sodium, chloride and phosphorus were observed, all signs of dehydration. Dehydration and metabolic acidosis, associated with reduced water and food intake contributed to the early demise of a number of animals 48 h post dose. Dehydration and metabolic acidosis were not observed in diabetic rats treated for 14 days with food provided *ad libitum*. Signs of metabolic ketoacidosis were not evident in repeat dose toxicity studies in rats (where animals had free access to food and water). Mild decreases in serum bicarbonate (13–22%) were seen in male dogs in which food was rationed. Metabolic ketoacidosis was seen in juvenile rats treated with dapagliflozin (≥1 mg/kg/day PO; ER_{AUC}, 16) (see *Use in children*). The metabolic acidosis occurred in diabetic animals and juvenile animals, suggesting that these groups are more susceptible to decreases in serum glucose than adult or non diabetic animals. These findings suggest a requirement for adequate fluid intake and possible monitoring for ketosis in diabetic patients.

Reduced body weight gain was seen in rats at ≥25 mg/kg/day PO (ER_{AUC}, 457) despite the increase in food consumption. Reduced body weight gain or body weight loss was seen in dogs treated with ≥5 mg/kg/day PO (ER_{AUC}, 142). These body weight changes were not considered adverse in adult animals. When food intake was restricted to prevent

[12] Food available at all times with the quantity and frequency of consumption being the free choice of the animal.

[13] Ly, J.P., T. Onay, K. Sison, G. Sivaskandarajah, V. Sabbisetti, L. Li, J.V. Bonventre, A. Flenniken, N. Paragas, J.M. Barasch, S.L. Adamson, L. Osborne, J. Rossant, J. Schnermann and S.E. Quaggin. (2011) The *Sweet Pee* model for Sglt2 mutation. *J. Am. Soc. Nephrol.* **22:** 113–123.

[14] Vallon, V., K.A. Platt, R. Cunard, J. Schroth, J. Whaley, S.C. Thomson, H. Koepsell and T. Rieg. (2011) SGLT2 mediates glucose reabsorption in the early proximal tubule. *J. Am. Soc. Nephrol.* **22:** 104–112.

hyperphagia, body weight loss (12%) was seen in dietary induced obese rats treated with 5 mg/kg/day PO dapagliflozin for 25 days in a pharmacology study (estimated ER_{AUC}, 49[15]). An increase in serum ketone bodies accompanied this body weight change, suggesting the animals were moving to a catabolic state.

Adrenal gland

Rats treated with ≥5 mg/kg/day PO dapagliflozin for 6 months (ER_{AUC}, 91) had increased absolute and bodyweight relative adrenal weights, with an increased incidence and severity of hypertrophy in the zona glomerulosa detected microscopically. Increased adrenal weights were seen in dogs treated with ≥5 mg/kg/day PO dapagliflozin (ER_{AUC}, 118) but without histopathological correlates. These adrenal changes are likely secondary to the electrolyte changes as a result of the diuretic effect and a compensating increase in aldosterone levels. Increased aldosterone levels have been reported in individuals with mutations in *SLC5A2* (the gene encoding SGLT2).[16] These adrenal changes were reversible and are not considered adverse.

Hypercalcaemia, vascular mineralisation and effects on bone and the GI system

Hypercalcaemia was observed in rats treated with ≥150 mg/kg/day PO dapagliflozin (ER_{AUC} at the no observable effect level (NOEL) 457) but not in dogs treated with ≤250 mg/kg/day PO dapagliflozin (ER_{AUC}, 5172). The hypercalcaemia in rats occurred in conjunction with increased urinary calcium excretion and changes in bone (increased bone mineral density and content, increased bone strength and increased trabecular bone volume). Urinary deoxypyridinoline levels (bone resorption marker) were decreased. These findings indicate that the hypercalcaemia was not associated with decreased urinary excretion of calcium or mobilisation from bone. Decreased circulating levels of 1,25-dihydroxyvitamin D, parathyroid hormone and calcitonin were also found, reflecting changes in calcium homeostasis. All of these findings are consistent with an increase in calcium absorption from the gut.

SGLT2-knockout mice do not display hypercalcaemia[14], suggesting it is not an effect of the pharmacological activity of dapagliflozin on SGLT2. Hypercalcaemia was not observed in dapagliflozin treated rats fed on a glucose-free diet (that is, substituted with fructose). Fructose is absorbed from the gut via the facilitative sugar transporter GLUT5 and not the glucose/galactose transporter, SGLT1.[17] On the glucose free diet, rats excreted much lower levels of calcium in urine. *In vitro* studies indicated dapagliflozin had some inhibitory activity at the rat SGLT1 transporter. Inhibition of SGLT1 while on a glucose/galactose diet leads to the accumulation of monosaccharides for intestinal bacteria to ferment, resulting in a decrease in pH with a corresponding increase in ionised calcium in the intestinal contents and an increase in intestinal calcium absorption.[18] Vascular mineralisation in multiple organs (including heart and kidney) was observed in rats treated with ≥150 mg/kg/day PO dapagliflozin for greater than 3 months. The finding is consistent with being secondary to the hypercalcaemia. Supporting this, neither hypercalcaemia nor vascular mineralisation were seen in dogs at ≤250 mg/kg/day PO dapagliflozin. Renal medullary tubular degeneration in rats is a known adverse effect of hypercalcaemia and nephrocalcinosis has been reported in individuals with a defective SGLT1 transporter.[3]

[15] Based on data in Study DN03049.

[16] Calado, J., J. Loeffler, O. Sakallioglu, F. Gok, K. Lhotta, J. Barata and J. Rueff. (2006) Familial renal glucosuria: *SLC5A2* mutation analysis and evidence of salt-wasting. *Kidney Internat.***69:** 852–855.

[17] Wright, E.M., M.G. Martin and E. Turk. (2003) Intestinal absorption in health and disease – sugars. *Best Pract. Res. Clin. Gastroenter.* **17:** 943–956.

[18] Guéguen, L. And Pointillart, A. (2000) The bioavailability of dietary calcium. *J. Am. College Nutr.* **19:** 119S–136S.

Clinical signs of diarrhoea, gaseous caecal content and hunched posture with microscopic findings of mineralisation of the stomach and caecal mucosa were found in rats treated at high doses (≥150 mg/kg/day) and are consistent with an increase in intestinal microbial activity secondary to glucose malabsorption. Dogs also showed marked increases in diarrhoea and emesis at high doses (≥120 mg/kg/day). Severe diarrhoea has been reported in human subjects with a defective SGLT1 transporter if they are not maintained on a glucose/galactose free diet .[19] As signs of SGLT1 inhibition occurred at high doses in rats (750 times the clinical dose on a mg/kg basis in a 50 kg patient) and dogs (600 times), and the selectivity of dapagliflozin for the SGLT2 transporter relative to the SGLT1 transporter is significantly greater in humans than in the laboratory animal species (917 times in humans compared to 207 times in rats and 436 times in dogs), glucose malabsorption and its associated side effects (diarrhoea, hypercalcaemia, vascular mineralisation and increased bone formation) are not expected to occur at the proposed clinical dose.

Urinary system

Dapagliflozin induced glucosuria, osmotic diuresis, hypercalciuria and natriuresis (see *Safety pharmacology*). These findings are consistent with the pharmacological effect of dapagliflozin. Proteinuria was seen in rats at low doses (≥5 mg/kg/day PO; ER_{AUC}, ≥91), but only at high doses in dogs (≥120 mg/kg/day PO; ER_{AUC}, ≥2888). Investigative studies demonstrated that dapagliflozin had no significant effect on protein endocytosis in a porcine renal cell line and that the proteinuria in rats was not associated with increased albumin or microalbuminuria, indicating no loss of glomerular integrity. The proteinuria in rats at low doses was not accompanied by histopathological changes in the kidney or increased serum creatinine levels, suggesting the finding is not a sign of nephrotoxicity. In another investigative study, increased urinary excretion of N-acetyl-β-D-glucosaminidase (a potential marker of proximal tubular cell injury) was observed in rats but histopathological examination revealed no treatment-related renal lesions. It is noted that proteinuria with increased levels of N-acetyl-β-D-glucosaminidase excretion in the absence of kidney damage has been seen in rats given various diuretics.[20, 21] The proteinuria in dogs at high doses occurred in the absence of correlating microscopic changes in the kidney and is likely associated with increased urinary output.

Increased kidney weights were seen at all doses in rats (≥5 mg/kg/day PO; ER_{AUC}, 91) and dogs (≥5 mg/kg/day PO; ER_{AUC}, 118). Microscopic examination revealed tubular dilatation in rats at ≥50 mg/kg/day PO (ER_{AUC} at the NOEL, 457) and an increased incidence and severity of renal pelvic dilation in male mice treated with ≥5 mg/kg/day (ER_{AUC}, 5) and female mice treated with ≥2 mg/kg/day PO dapagliflozin (ER_{AUC}, 12) for up to 2 years. An increased incidence of urinary bladder distension/dilatation was seen in male mice at ≥15 mg/kg/day PO dapagliflozin (ER_{AUC}, 15) and in male rats at 10 mg/kg/day PO dapagliflozin (ER_{AUC}, 169) with treatment for up to 2 years. All of these renal and bladder findings are likely associated with the increased urinary output and workload associated with the elimination of increased amounts of glucose. Increased kidney weights were still seen in rats after a 3-month treatment-free period.

[19] Turk, E., B. Zabel, S. Mundlos, J. Dyer and E.M. Wright. (1991) Glucose/galactose malabsorption caused by a defect in the Na^+/glucose cotransporter. *Nature* **350:** 354–356.

[20] Kutina, A.V., V.V. Zakharov and Y.V. Natochin. (2008) Excretion of proteins by rat kidney during various types of diuresis. *Bull. Exp. Biol. Medicine* **146:** 671–674.

[21] Lina, B.A.R., H.M. Bos-Kuijpers, H.P. Til and A. Bar. (1996) Chronic toxicity and carcinogenicity study of erythritol in rats. *Regul. Toxicol. Pharmacol.* **24:** S264–S279.

An increase in the severity of chronic progressive nephropathy (CPN) was seen in male rats treated with ≥0.5 mg/kg/day PO dapagliflozin (ER_{AUC}, 8) in the 2 year carcinogenicity study and in female rats only in the pivotal 6 month study at 150 mg/kg/day PO (ER_{AUC}, 2337). The incidence and severity of cortical tubule epithelium vacuolation and atypical tubule hyperplasia were also seen to be increased in male rats in the carcinogenicity study, consistent with the histopathology of CPN.[22] The higher incidence of pre terminal deaths in males at 10 mg/kg/day in the rat carcinogenicity study was attributed to an exacerbation of CPN. CPN occurs in high incidence in male Sprague-Dawley rats and it has no clear human counterpart.[22] The exacerbation of CPN in male rats with dapagliflozin may be the result of alterations in the diet, in renin-angiotensin levels and/or filtration alterations[22], rather than a direct nephrotoxic effect. The absence of similar findings in mice treated with ≤40 mg/kg/day PO dapagliflozin (ER_{AUC}, at least 78) for 2 years or in dogs treated with ≤120 mg/kg/day PO dapagliflozin for 12 months (ER_{AUC}, 2888) further confirms the exacerbation of CPN is not related to a nephrotoxic effect and is unlikely to be clinically relevant.

Urothelial hyperplasia was seen in the kidneys of rats treated with 150 mg/kg/day PO dapagliflozin (ER_{AUC}, 2337) for 6 months and in the kidney or bladder of a number of treated dogs in the 12 month study. There was no apparent relationship with dose in dogs and due to the presence of inflammatory cells was suggested to be associated with urinary tract infections. Urothelial hyperplasia is recognised as a response to chronic urinary tract infections in rats.[23] Bacterial infections were seen in the kidney and urinary bladder of a single treated rat at 5 mg/kg/day PO dapagliflozin (ER_{AUC}, 49) for 1 month. Tetracycline was administered at a number of intervals in toxicity studies for bone analyses. The administration of antibiotics may have minimised the likelihood of urinary tract infections. The increased urinary excretion of glucose may promote urinary tract infections. As a similar extent of glucosuria was seen at all tested doses, a dose response may not be seen. Diabetic SGLT2-knockout mice had a high incidence of urinary tract infections, leading to premature deaths.[13] Urinary tract infections were not seen in non diabetic SGLT2-knockout mice or diabetic wild-type mice, suggesting that diabetic SGLT2-knockout mice for some unknown reason are more prone to urinary tract infections. The potential for dapagliflozin to increase the susceptibility of patients to urinary tract infections requires particular attention by the clinical evaluator.

Combination studies

No studies have been conducted to assess the potential toxicological interactions between dapagliflozin and other anti-diabetic drugs proposed to be used as co therapies.

Genotoxicity

The potential genotoxicity of dapagliflozin was investigated in the standard battery of tests, and an *in vivo* study on unscheduled deoxyribonucleic acid (DNA) synthesis. All assays were appropriately validated and the conduct of the studies was in accordance with TGA adopted EU guidelines.[24] All *in vivo* studies involved oral administration to rats. Dapagliflozin, in the presence of metabolic activation (rat S9) was consistently clastogenic *in vitro* in Chinese hamster ovary cells at non cytotoxic concentrations. There was no

[22] Hard G. C. Johnson K. J. Cohen S. M. (2009). A comparison of rat chronic progressive nephropathy with human renal disease—Implications for human risk assessment Crit. Rev. Toxicol 39 332–346.

[23] Davis, C.P., M.S. Cohen, M.B. Gruber, M.D. Anderson and M.M. Warren. (1984) Urothelial hyperplasia and neoplasia: a response to chronic urinary tract infections in rats. *J. Urol.* **132:** 1025–1031.

[24] CPMP/ICH/174/95 Topic S2B; Genotoxicity: A standard battery for genotoxicity testing of pharmaceuticals. http://www.tga.gov.au/pdf/euguide/ich017495en.pdf

evidence of clastogenicity in the absence of metabolic activation. The clastogenic metabolite was not identified. The *in vivo* clastogenicity of dapagliflozin was assessed in several micronucleus assays in rats with daily dosing for between 3 days and up to 1 month. Doses chosen were up to toxic levels and achieved exposures of dapagliflozin up to 2500 times the clinical exposure and estimated dapagliflozin 3-O-glucuronide exposures 5 times higher than that expected clinically. No significant increase in the frequency of micronucleated cells was seen in the bone marrow (in 3 day and 2 week studies) and no significant increase in structural aberrations was seen in peripheral blood lymphocytes (in the 1 month study). Negative results were also obtained in the bacterial mutagenicity assay and the unscheduled DNA synthesis study. The balance of evidence indicates that dapagliflozin is unlikely to be genotoxic.

Carcinogenicity

The carcinogenic potential of dapagliflozin by the oral route was investigated in 2 year studies in CD-1 mice and SD rats (GLP-compliant). Group sizes were appropriate and dual control groups were used, as recommended in the TGA adopted EU guideline on carcinogenic potential (3BS7a).[25]

Survival was modestly reduced at the two highest doses in males in the mouse study (≥15 mg/kg/day) and in the rat study the mortality rate was high in all male groups (including the control groups, prompting early termination in week 90). Most of these groups had less than the desired number of surviving animals (approximately 25) at the scheduled necropsy (as specified in EU guideline 3BS7a). Based on there being an adequate number of animals that survived to 18 months treatment, the studies are considered acceptable and the early termination of the surviving male animals is not considered to critically impact the reliability of the rat study. The relative exposures to dapagliflozin at the highest tested doses in both studies were sufficiently high (78–112 and 169 times the clinical AUC in mice and rats, respectively). No treatment related increase in tumour incidence was observed in either study. The negative genotoxicity and carcinogenicity findings suggest a low carcinogenic potential for dapagliflozin.

Estimated exposures to dapagliflozin 3-O-glucuronide achieved at the highest doses in the rodent carcinogenicity studies were similar or below that expected clinically. Consequently, the studies are not considered adequate to have assessed the carcinogenic potential of the major human metabolite. In response to an information request, the sponsor provided a comment on the genotoxic and carcinogenic potential of this metabolite. Dapagliflozin 3-O-glucuronide is a stable ether glucuronide which, unlike acylglucuronides, is not susceptible to nucleophilic substitution. Dapagliflozin 3-O-glucuronide was not pharmacologically active across >300 targets and this metabolite does not have any structural alerts for mutagenicity. Dapagliflozin 3-O-glucuronide levels were sufficiently high in repeat-dose toxicity studies with no clear indication of a pre neoplastic effect. As outlined in the *FDA Guidance for Industry on Safety Testing of Drug Metabolites*[26], this type of modification (glucuronidation) generally results in a water soluble, pharmacologically inactive metabolite, which often eliminates the need for further evaluation. Based on the arguments provided by the sponsor, the weight of evidence indicates a low carcinogenic potential for this human metabolite.

Isolated incidences of urothelial hyperplasia in the kidney and/or bladder were observed in rat and dog toxicity studies and were attributed to urinary tract infections (see *Repeat-dose toxicity*). Urothelial hyperplasia and bladder cancer are known to occur in response to chronic urinary tract infections in rats.[23, 27] Urinary tract infections were not common in

[25]See http://www.tga.gov.au/industry/pm-euguidelines-adopted-nonclinical.htm
[26] http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0065-GDL.pdf
[27] Michaud, D.S. (2007) Chronic inflammation and bladder cancer. *Urol. Oncol. Semin. Orig. Invest.* **25:** 260–268.

normoglycaemic animals in the toxicity studies. Diabetic SGLT2 knockout mice were more prone to urinary tract infections than their non diabetic counterparts.[13] The use of an SGLT2 inhibitor, such as dapagliflozin, may indicate a higher risk of urinary tract infections and possibly urothelial lesions (including bladder cancer) associated with chronic inflammation. It is noted that the incidence of urinary tract infections was higher in the dapagliflozin-treated groups than the placebo control groups in clinical trials.

Reproductive toxicity

A standard set of GLP compliant reproductive toxicity studies was submitted and examined potential effects on male and female fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used in the pivotal studies, and treatment periods were appropriate. Toxicokinetic data were obtained either from animals in the studies or from similarly treated animals in accompanying studies. Exposure levels for dapagliflozin achieved were significantly greater than the clinical exposure (Table 3). Estimated exposure ratios for dapagliflozin 3-O-glucuronide have also been calculated for the studies in rats, based on being 0.36% that of its parent (no data are available to assess exposure to this metabolite in rabbits).

Decreased epididymal and seminal vesicle weights with altered spermatogenesis (reduced sperm counts and motility, and an increase in morphologically abnormal sperm) were seen in male rats treated with 210 mg/kg/day PO dapagliflozin (NOEL 75 mg/kg/day; ER_{AUC}, 717). There was no apparent effect on mating or on fertility when the treated males were paired with untreated females. Given the large safety margin, an adverse effect on male fertility is not predicted at the proposed clinical dose. Female fertility was unaffected in rats treated with ≤75 mg/kg/day PO dapagliflozin (ER_{AUC}, 1059) but an increase in postimplantation loss was observed at ≥15 mg/kg/day PO (NOEL, 3 mg/kg/day; ER_{AUC}, 41).

Dapagliflozin crossed the placenta in rats with significant exposures seen in the fetal circulation. An increased incidence of embryofetal lethality and fetal visceral (absent innominate artery and positional defects of the aorta and arteries) and skeletal anomalies (incomplete ossification, duplicated or fused bones) together with reduced fetal weight were seen in rats treated at ≥150 mg/kg/day PO. These findings occurred in the context of maternotoxicity and are unlikely to be an indication of a direct drug-related effect. The NOEL for embryofetal effects in rats was 75 mg/kg/day PO (ER_{AUC}, 1530). Of note, though, an increased incidence of renal pelvic dilatation was seen in pups exposed to dapagliflozin *in utero* and during the lactation period in a pre/postnatal study, suggesting that dapagliflozin may have an effect on kidney development (see below). No drug related embryofetal effects were seen in rabbits treated with ≤180 mg/kg/day PO dapagliflozin (ER_{AUC}, 1265).

Table 3. Relative exposure in reproductive toxicity studies

Species & strain; Study			Dose (mg/kg/day) PO	AUC0–24 h (µg·h/mL)		Exposure ratio	
				Dapagliflozin	Dapagliflozin 3-O-glucuronide	Dapagliflozin	Dapagliflozin 3-O-glucuronide
Rat (SD)	DN04014 *[fertility]*	males	15	74.4	0.27	170	0.3
			75	314	1.13	717	1.4
			210	794	2.86	1813	3.6

Species & strain; Study			Dose (mg/kg/day) PO	AUC0–24 h (µg·h/mL)		Exposure ratio	
				Dapagliflozin	Dapagliflozin 3-O-glucuronide	Dapagliflozin	Dapagliflozin 3-O-glucuronide
		non-pregnant females	3	18.1	0.07	41	0.08
			15	87.3	0.31	199	0.4
			75	464	1.67	1059	2.1
	DN05081 *[embryofetal development]*	pregnant females	150	1590	5.72	3630	7.1
			225	1380	4.97	3151	6.2
			300	1900	6.84	4338	8.5
	DN04052 *[embryofetal development; supportive]*	pregnant females	37.5	327	1.18	747	1.5
			75	670	2.41	1530	3.0
			150	1090	3.92	2489	4.9
			300	1840	6.62	4201	8.2
	DN09008 *[pre-/postnatal development]*	lactating females	1	8.7	0.03	20	0.04
			15	116	0.42	265	0.5
			75	658	2.37	1502	2.9
Rabbit (NZW)	DN04051 *[embryofetal development; supportive]*	pregnant females	20	30	NA	68	–
			60	138	NA	315	–
			180	554	NA	1265	–
Human	MB102027		[10 mg]	0.438	0.803	–	–

– = not relevant; NA = not available

In a pre/postnatal study in rats, parturition and gestation length were unaffected by dapagliflozin treatment (≤75 mg/kg/day PO; ER_{AUC}, 1500). Dapagliflozin (and possibly its metabolites) were excreted into milk in rats and dapagliflozin could be detected in the circulation of breastfed pups following maternal dosing. The offspring of dams treated with dapagliflozin during gestation and lactation had reduced birth weights (at 75 mg/kg/day) and reduced postnatal weight gain (≥15 mg/kg/day), consistent with observations in SGLT2-knockout animals, suggesting pharmacological activity in these pups. An increased incidence of renal pelvic dilatation was observed in pups at 75 mg/kg/day PO (ER_{AUC}, 1500) at necropsies conducted 3 months after the end of drug exposure. Renal pelvic dilatation and tubular dilatation were observed in a study in

juvenile rats with treatment at ≥1 mg/kg/day PO dapagliflozin (ER_{AUC}, at least 16; NOEL not established) and these were seen to be irreversible (1 month recovery period). The findings may be associated with the reduced ability of the developing kidney to handle the increased urinary output induced by dapagliflozin. Kidney anatomical maturation occurs postnatally in rats, with nephrogenesis continuing to 11 days from birth[28] and tubular differentiation continuing until the time of weaning (~21 days of age); functional maturation occurs later still. Human anatomic renal maturation occurs *in utero* during the second and third trimesters and functional maturation continues for the first 2 years of life.[29] As such, the finding of irreversible kidney changes in rat pups suggests a risk to renal development in humans during the second and third trimester and the first 2 years of life. Motor activity, learning and memory and sensory function of pups were unaffected by maternal treatment. Female sexual development was also not affected but delayed pubertal development was seen in males following maternal exposure (≥15 mg/kg/day PO dapagliflozin; ER_{AUC}, 265) or following direct exposure (≥1 mg/kg/day PO; ER_{AUC}, at least 16; NOEL not established). Delayed growth and pubertal development have been reported in a human male individual with a homozygous mutation in the SGLT2 gene (*SLC5A2*)[30], suggesting the delayed male pubertal development may be secondary to the pharmacological activity of dapagliflozin. Given its excretion into milk and the possibility of adverse effects on the growth and development of breastfed infants, dapagliflozin should not be used by women who are breastfeeding.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3. However, given the irreversible kidney changes and their applicability to the time of gestation in humans, Category D is considered to be more appropriate. This category is for drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage.

Use in children

A toxicity study in juvenile rats was conducted to determine the potential for toxicity in the paediatric population. Treatment was for 2 months and the developmental age of the rats (3 weeks of age at the commencement of the study and 12 weeks at the completion of dosing) approximately correlates with children to adolescents (2 to ~16 years[31]). Delayed growth was seen with treatment at 75 mg/kg/day (ER_{AUC}, at least 1150) and delayed pubertal development was seen in males at ≥1 mg/kg/day PO dapagliflozin (ER_{AUC}, at least 16; NOEL not established). Juvenile rats appeared to be more prone to hypoglycaemia than adults with decreased serum glucose (22–48%) and signs of metabolic acidosis (decreased serum carbon dioxide, triglyceride and cholesterol, and increased urinary ketones) seen in animals treated with ≥15 mg/kg/day PO dapagliflozin (ER_{AUC}, ≥221). An increase in serum urea also indicated a shift to a catabolic state. Pancreatic zymogen granule depletion and an increased incidence of minimal mucosal haemorrhage and minimal to slight ulceration or erosion of the glandular mucosa of the stomach detected at necropsy in juvenile rats treated with ≥15 mg/kg/day PO dapagliflozin (NOEL, 1

[28] Kavlock, R.J and J.A. Gray. (1982) Evaluation of renal function in neonatal rats. *Biol. Neonate* **41:** 279–288.

[29] Zoetis, T. and M.E. Hurtt. (2003) Species comparison of anatomical and functional renal development. *Birth Defects Res. (Pt B)* **68:** 111–120.

[30] Scholl-Burgi, S., R. Santer and J.H. Ehrich. (2004) Long-term outcome of renal glucosuria type 0: the original patient nd his natural history. *Nephrol. Dial. Transplant* **19:** 2394–2396.

[31] Baldrick , P. (2004) Developing drugs for paediatric use: a role for juvenile animal studies? *Reg. Toxicol. Pharmacol.* **39:** 381–389.

mg/kg/day; ER_{AUC}, at least 16) are all signs of fasting and food deprivation. Taken together, these findings suggest that juvenile rats are more susceptible to hypoglycaemia than adults and do not easily adapt to the changes in glucose handling. As with dapagliflozin treated adult rats, juveniles had hypercalcaemia with follow-on effects on the kidney (mineralisation) and bone (increased one formation). Dapagliflozin treated juvenile rats (at ≥1 mg/kg/day PO; ER_{AUC}, at least 16; NOEL not established) also had irreversible renal pelvic dilatation, probably secondary to increased urinary output. Due to the irreversible nature, the findings indicate that dapagliflozin treatment to children may have adverse effects on kidney development (see *Reproductive and developmental toxicity*).

While only minor differences in dapagliflozin exposure were seen between immature and adult rats at comparable doses, this is unlikely to reflect the clinical situation. The major metabolic pathway for dapagliflozin in human subjects is glucuronidation via the predominantly extra-hepatically expressed UGT1A9 to form the inactive metabolite, dapagliflozin 3-O-glucuronide. This was not a prominent pathway in rats. UGT1A9 expression shows an age dependent increase in expression in the liver of paediatric patients and its levels do not reach those in adults even by 2 years of age.[32] Presumably the levels of UGT1A9 in the kidney follow a similar pattern. This, taken together with a prominent role of the kidney in the clearance of dapagliflozin and with the kidney not reaching functional maturation until at least 2 years of age, warrants particular caution for any use of dapagliflozin in paediatric patients below 5 years of age.

Local tolerance

Local tolerance studies were adequately conducted and revealed no irritation following topical dermal application to rabbits or IV injection in dogs. Hindlimb swelling and slight focal necrosis at the injection site was observed following SC administration to dogs. Dapagliflozin was conservatively estimated as a moderate to severe ocular toxicant in an *in vitro* study with bovine corneas (reflecting technical difficulties in the assay). Dapagliflozin was not a skin sensitiser in the mouse local lymph node assay.

Nonclinical summary and conclusions

- The overall quality of the submitted nonclinical data was high, with all pivotal toxicity studies conducted under GLP conditions and using the proposed clinical route (PO). No nonclinical studies on pharmacokinetic or toxicological interactions with the proposed combination therapies were included in the submission.
- Dapagliflozin belongs to a novel pharmacological class. *In vitro*, dapagliflozin inhibited SGLT2 with nanomolar potency. SGLT2 is a sodium-glucose co-transporter that has a major role in glucose reabsorption in the kidney. *In vivo*, at exposures similar to that expected clinically, dapagliflozin reduced plasma glucose levels in diabetic rats. There was no effect on insulin levels. Studies in rats indicated dapagliflozin may delay the progression of Type 2 diabetes.
- There was no significant inhibition of the facilitative glucose transporters, GLUT1, GLUT2 and GLUT4 or 40 different receptors, enzymes and/or ion channels at concentrations up to at least 10 μM. The selectivity of dapagliflozin for SGLT2 over SGLT1was approximately 900 to 3000 fold.
- No significant inhibition of the hERG K^+ channel was observed (at up to 333 times the clinical unbound C_{max}). No effect on action potential duration was seen in experiments

[32] Strassburg, C.P., A. Strassburg, S. Kneip, A. Barut, R.H. Tukey, B. Rodeck and M.P. Manns. (2002) Developmental aspects of human hepatic drug glucuronidation in young children and adults. *Gut* **50:** 259–265.

with rabbit Purkinje fibres and no abnormalities in ECG parameters were seen in dogs (at 1290 times the clinical C_{max}). No effects on the CNS or respiratory system were identified in the general toxicity studies at very high exposure margins.

- For the most part, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Dapagliflozin was rapidly absorbed (T_{max}, 0.5–1.9 h) with high oral bioavailability in rats, dogs and humans (78–84%). Plasma protein binding by dapagliflozin was high in animals and humans and tissue distribution of dapagliflozin and/or its metabolites in rats was widespread. Unchanged dapagliflozin was the main circulating drug related compound in animal species, while both dapagliflozin and the UGT1A9 derived metabolite dapagliflozin 3-O-glucuronide (pharmacologically inactive) were the main drug related compounds in human plasma. *In vitro* experiments showed that metabolism by CYPs was not a prominent degradative pathway in humans. Drug related material was excreted roughly equally in the urine and faeces in rodents, predominantly in the faeces of dogs and in the urine in humans.
- There was no clinically significant inhibition of the human CYP450 isozymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) or transporters (P-glycoprotein, hOCT2, hOAT1 or hOAT3) or induction of CYP1A2, 2B6 or 3A4, with dapagliflozin *in vitro*. Dapagliflozin is not expected to alter the pharmacokinetics of co administered drugs. As dapagliflozin is chiefly metabolised by UGT1A9, inhibitors or inducers of UGT1A9 may affect the plasma kinetics of dapagliflozin. Some variability in dapagliflozin exposure may be seen in patients containing one of a number of naturally occurring polymorphisms of the UGT1A9 gene (or flanking region) which affects the activity or expression level of this enzyme.
- Dapagliflozin had a low order of acute oral toxicity in mice, rats and dogs.
- Repeat dose toxicity studies were performed in mice, rats and dogs using the clinical route (PO) with very high relative exposures to dapagliflozin achieved. Relative exposures to dapagliflozin 3-O-glucuronide were modest in rodents (generally ≤20 times the clinical AUC) and high in dogs (≤150 times the clinical AUC). The pivotal studies were of 6 months duration in rats and 12 months in dogs. Target organs for toxicity were the urinary system, adrenals and bones in rats, with vascular mineralisation observed in multiple organs. No consistent target organs were identified in the other species.
- Dapagliflozin had an osmotic diuretic effect in all species and at all doses tested and induced an increase in food and water consumption. Signs of dehydration and metabolic ketoacidosis were only seen at high doses in dapagliflozin treated diabetic rats and in conjunction with decreased food and water intake. Reduced body weight gain was occasionally seen. Treatment was associated with adrenal changes in rats and dogs, likely secondary to increased demand for aldosterone due to diuresis and not considered adverse. Hypercalcaemia with multi organ mineralisation and increased bone formation was only seen in rats at high oral doses (the NOEL being 457 times the clinical AUC). A dose related increase in severity of chronic progressive nephropathy was seen in male rats treated for 2 years (at ≥8 times the clinical AUC). Urinary tract infections or histopathological changes consistent with urinary tract infection were observed in dapagliflozin treated rats and dogs and an increased incidence of urosepsis in diabetic mice with an impaired SGLT2 transporter has been reported in the literature.
- The potential genotoxicity of dapagliflozin was investigated in the standard battery of tests and in an *in vivo* study on unscheduled DNA synthesis. Dapagliflozin in the presence of metabolic activation was clastogenic *in vitro* but there was no evidence of clastogenicity in the absence of metabolic activation or in *in vivo* studies in rats at high oral doses (≤2500 times the clinical AUC). Negative results were obtained in the

remaining assays. The weight of evidence indicates that dapagliflozin is unlikely to be genotoxic.

- No treatment related increase in tumour incidence was observed in mice or rats in 2 year oral carcinogenicity studies. Doses achieved high relative exposures to dapagliflozin (≤169 times the clinical AUC) but estimated exposures to dapagliflozin 3-O-glucuronide were similar to or below that expected clinically.
- Decreased epididymal and seminal vesicle weights with altered spermatogenesis were seen in dapagliflozin treated male rats at very high doses (the NOEL being 717 times the clinical AUC). No adverse effects on fertility were evident in treated female rats. In rats, dapagliflozin was readily transferred across the placenta and excretion into milk was high. Dapagliflozin could be detected in the circulation of breastfed pups. An increased incidence of irreversible renal pelvic dilatation was seen in the offspring of rats treated with dapagliflozin during gestation and lactation (at ~1500 times the clinical exposure) as well as in juvenile rats treated directly with dapagliflozin (NOEL not established). Delayed growth was seen in breastfed pups. Delayed pubertal development was seen in males following maternal exposure and in juvenile males treated directly with dapagliflozin (NOEL not established). Embryofetal lethality and an increased incidence of fetal abnormalities were seen only at maternotoxic doses in rats (NOEL, >1500 times the clinical exposure), while no adverse embryofetal effects were seen in rabbits (at >1200 times the clinical exposure).
- Dapagliflozin treated juvenile rats were more prone to hypoglycaemia and metabolic acidosis than adults, and had delayed growth.

Conclusions and recommendations

- Primary pharmacology studies showing a reduction in plasma glucose levels and an improvement in insulin sensitivity support the drug's use for the proposed indication.
- No clinically significant off-target activities are predicted based on secondary pharmacology studies.
- Given the extensive role of the kidney in the clearance of dapagliflozin, greater dapagliflozin exposure may be seen in patients with renal impairment. Reduced efficacy may also be expected. Given the major role of UGT1A9 in the metabolism of dapagliflozin, inducers or inhibitors of this enzyme may affect the plasma kinetics of dapagliflozin.
- Increased urine output and glucosuria indicate a risk for dehydration and ketosis in diabetic patients.
- Hypercalcaemia and the exacerbation of chronic progressive nephropathy observed in rats are not considered to indicate likely hazards in humans.
- Findings of urothelial lesions in treated animals, consistent with urinary tract infections and the increased incidence of urosepsis reported in diabetic SGLT2 knockout mice indicate a risk for urinary tract infections in patients with Type 2 diabetes.
- Dapagliflozin is not considered to pose a genotoxic or carcinogenic hazard to patients.
- Reproductive toxicity and juvenile animal studies in rats indicate a risk for adverse effects on kidney development, warranting particular caution with use in pregnancy and lactation.
- The findings in juvenile animal studies raise concerns for any future paediatric indication.

- There are no objections on nonclinical grounds to the registration of dapagliflozin as monotherapy for the proposed indication. In the absence of nonclinical data regarding dapagliflozin in combination with other anti-diabetic agents, the safety of the proposed combinations will need to be addressed by clinical data alone.

It was also recommended that the PI document be updated.

IV. Clinical findings

Introduction

Throughout the application, studies with the prefix MB have been carried out by or on behalf of Bristol-Myers Squibb (BMS) and those with the prefix D, AstraZeneca (AZ).

The program as presented in this application comprises reports of 26 completed studies of the pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin, as well as another which was not proceeded with, and 14 reports of Phase IIb and Phase III clinical studies, some of which have ongoing extensions.

Good clinical practice aspects

All of the studies in the application describe appropriate procedures for ethical study conduct including giving of information and consent arrangements, counselling, and clinical care when appropriate, consistent with relevant international guidelines. The documentation of these procedures is highly consistent between the various studies and overall compliance with Good Clinical Practice (GCP) throughout the development program appears satisfactory.

The second round evaluation mentions the following:

In the section *List of Questions* below there is a report on errata in Study MB 102059, which was evaluated in the first round CER.

In the section *List of Questions* below there is a 50 week report of Study D1690C00012, also evaluated in the first round CER, which requires comment regarding the issue of bone safety.

Pharmacokinetics

Introduction

The 26 clinical pharmacology studies involved the participation of 688 subjects. The sponsor states that 635 of these were exposed to dapagliflozin, although the "head count" in this evaluation is 632. These were mostly healthy adults but included subjects with T2DM (118 subjects, 101 of whom were exposed to dapagliflozin) and subjects with renal or hepatic impairment (20 and 18 subjects respectively, all exposed to dapagliflozin). The application includes 8 single and multiple dose studies, in which single oral doses from 2.5 to 500 mg and multiple oral doses from 2.5 to 100 mg of dapagliflozin for up to 14 days were evaluated in healthy subjects. Multiple oral doses from 5 to 100 mg of dapagliflozin for up to 14 days were evaluated in subjects with T2DM. In addition, 4 studies were conducted in special populations and 4 bioavailability/bioequivalence and food interaction studies were conducted. Also included are 10 drug-drug interaction studies in healthy subjects evaluating dapagliflozin in combination with other oral anti-diabetic medications, commonly co-prescribed cardiovascular medications and with rifampicin, which is an inducer of several drug metabolising enzymes.

Methods

Analytical methods

Measurement of dapagliflozin levels and those of its metabolites in plasma and other body fluids was carried out using a liquid chromatography (LC)/mass spectrometry (MS) method. Assay performance is described in the individual study reports. The lower and upper limits of quantification (LLOQ, ULOQ) were generally 1.00 and 500 µg/mL respectively although in Study MB 102088 which involved very low doses of dapagliflozin, the assay was optimised to the low end with LLOQ 0.10 ng/mL. Between-run coefficient of variation (CV) values of between 2% and 5% are quoted and within-run CVs of 5% and 10%, along with quality control (external reference standard) data stated to meet predetermined criteria for accuracy and precision.

Pharmacokinetic data analysis

Procedures for blood sampling and the construction of plasma time/concentration profiles following administration of oral doses of dapagliflozin were standardised across most of the pharmacokinetic (PK) studies, all of which involve the assessment of the plasma dapagliflozin response to oral dosing in some way. Blood samples were taken at intervals of 15, 30, 45, 60 and 90 min and 2, 4, 8, 12, 16, 24, 36 and 48 h following dosing and subsequent longer intervals if required by the specific study protocol. From the dapagliflozin levels in the samples, the following PK parameters were estimated:

Cmax	maximum plasma concentration observed
Tmax	time to maximum plasma concentration
t½	terminal half life, calculated as ln(2)/Kel*
AUC 0-t	area under plasma concentration/time curve from time zero to last quantifiable value**, reflecting total drug exposure
AUC0-inf	area under the plasma concentration/time curve from time zero, extrapolated to infinity

*Kel is the terminal phase rate constant, calculated using linear regression from the terminal portion of the concentration/time curve. Calculation of this parameter has the potential to produce underestimated values for t½ if dapagliflozin levels towards the end of the elimination process are approaching or below LLOQ.

**In some studies, $AUC_{(TAU)}$ is used, denoting area under the plasma concentration time curve from time zero to end of treatment period. Given the relatively rapid absorption and elimination characteristics of dapagliflozin, the difference between the three methods of calculating AUC is minimal.

In graphic data displays throughout the application and reproduced in this report, plasma concentrations are presented as mean ± standard deviation (SD) on both linear and semilogarithmic scales.

Statistical analysis

General principles for data management and statistical analysis in the studies described in this section were the same as those for the efficacy studies, as described below under *Efficacy*.

When prespecified for testing, bioequivalence was concluded if the 90% confidence intervals (CI) for the ratios of the geometric means of the two treatments being tested were entirely contained within the bounds 0.80-1.25 for both C_{max} and $AUC_{0\text{-}inf}$.

Absorption

Bioavailability

The absolute bioavailability of dapagliflozin from oral administration of a 10 mg dose given to healthy adult males was *78%* (90% CI 73.2, 82.8), as shown in Study MB 102059. Data from mass balance Study MB 102006 are consistent with this.

Bioequivalence

There were no studies demonstrating bioequivalence of the 5 mg and 10 mg tablets. The sponsor offered a justification for this as follows:

- "the 5 and 10 mg formulations share the same granulation (direct scales) and dissolution profiles are the same across all pH values tested (0.1 N HCl, pH 4.8 buffer and pH 6.5 buffer)
- dapagliflozin is considered to be a BCS Class I-like compound with a high aqueous solubility relative to the highest proposed dose of 10-mg, high in vitro permeability, and good absolute oral bioavailability in humans (78%) with dose proportional oral pharmacokinetics over the clinically relevant dose range."

Equivalence of the 5 mg and 10 mg tablets is based on these pharmaceutical grounds only. The 5 mg doses given in the studies of dose proportionality were given using capsules or solution formulations.

Bioequivalence of a 50 mg tablet formulation and a 10 mg capsule formulation, which were in use at an early stage of product development and is used in some of the included studies, was demonstrated by Study BM 102005 although by strict criteria the study was not powered for this purpose.

Influence of food

Study BM 102019 showed an effect on initial absorption, with a reduction in C_{max} and delay in T_{max} from approximately 1 h to 2 h but there was *no effect on total drug exposure* following an oral dose of 10 mg dapagliflozin when administered immediately after a high-fat meal. PK parameters of an inactive metabolite of dapagliflozin, BMS 801576, were similarly affected. The lack of food effect on the PK of dapagliflozin was also observed following administration of tablets whose physicochemical characteristics had been altered by heat exposure (Study BM 102062). A slight (approximately 10%) reduction in exposure from a 2.5 mg tablet taken following the same high-fat meal was observed in Study MB 102090. This suggests that any such effect on the 5 mg tablet would not be at a clinically significant level.

Similar findings to the above were reported in Study BM 102001 in a small group of subjects receiving a single 250 mg dose.

Distribution

Following oral ingestion, dapagliflozin is absorbed rapidly and appears in the circulation with a T_{max} of approximately 1 h (Study MB 102005; 102004; 102006). It has a high volume of distribution, 118 L as estimated in Study MB 102059. The time characteristics of absorption are maintained across a wide range of doses up to 500 mg (Study MB 102001) and down to the very low dosage range 0.01 mg-2.5 mg given in Study MB102088.

Dapagliflozin is transported in plasma in protein bound form, with protein binding being estimated at 90-96% (Studies MB 102007 and MBA 102010) accounting for part of the high volume of distribution.

In all of the PK studies, there is as expected a relationship between dapagliflozin exposure as measured by a variety of AUC parameters and the dose given. This approximates 50

ng.h/mL of AUC per mg of dapagliflozin given and varies very little across the wide dose range (2.5-500 mg) and in the various populations studied. Where relevant in this report and in the review of the various PK studies, reference is made to this parameter of exposure per unit dose and to the index value of 50 ng.h/mL/mg for the purpose of comparison.

Elimination

Excretion

The major route of elimination for dapagliflozin is urinary excretion; following administration of radioactively (^{14}C) labelled dapagliflozin in mass balance Study MB 102006, 75% of the radioactivity was recovered in the urine, mostly in the first 24 h and in the form of metabolites, principally dapagliflozin 3-O-glucuronide. This major metabolite, which according to the sponsor's interpretation of the nonclinical data is metabolically inactive, is referred to in many parts of the application, particularly in early studies, as BMS 801576 but throughout this report will for clarity be referred to by its chemical name. Only some 1.5% of the dapagliflozin dose was excreted unchanged. In the mass balance study, most of the remaining radioactivity (21%) appeared in the faeces and of this, most (15% of administered dose) was in the form of unaltered dapagliflozin.

In Study MB 102025, urinary recovery of unchanged dapagliflozin was < 2%. Renal clearance of dapagliflozin was estimated at 4.3 mL/min (range 3.75 to 5.10). Renal clearance for dapagliflozin 3-O-glucuronide ranged from 130-152 mL/min and over 80% of administered drug was recovered in the form of this metabolite in the urine.

In Study MB 102010, renal clearance estimations for dapagliflozin were corrected for serum/plasma protein binding which was measured as 4% free/96% bound. This correction yielded a value of 87.5 mL/min, suggesting that the renal clearance of unbound dapagliflozin is mainly due to filtration.

Metabolism

Dapagliflozin has a minor metabolically active derivative, BMS-511926 which only achieves some 1% of the plasma levels of the parent drug; the largest component of dapagliflozin related substances present in plasma, some 70%, is accounted for by inactive metabolites (Study MB 102006 and Study 102017), mostly dapagliflozin 3-O-glucuronide the formation of which is catalysed by enzyme UGT1A9 (quoted in proposed PI). These inactive metabolites in urine accounted for approximately 75% of the administered radioactivity recovered in the mass balance study.

Conversion to the inactive metabolite dapagliflozin 3-O-glucuronide under the influence of UGT 1A9 occurs in both liver and kidney and is the major clearance pathway for dapagliflozin. CYP 450 metabolism is stated to be a minor clearance pathway only (quoted in proposed PI).

Pharmacokinetics of metabolites

Study MB 102017 examined the time concentration profiles for dapagliflozin 3-O-glucuronide. These proved similar to those for the parent drug dapagliflozin, with a T_{max} averaging 1.5 h but slightly longer $T_{½}$ values of approximately 15 h. Exposure in mass terms is shown to be approximately 2 fold that of the parent drug, mean $AUC_{(inf)}$ being 4488 ng.h/mL, consistent with the findings of Study MB 102006.

The pharmacologically active metabolite BMS-511926 circulates in only small quantities. In Study MB 102001, it accounted for < 0.2% of administered dapagliflozin doses recovered in the urine. On the basis of limited data, its PK appeared to be subject to the same food effect as that of the parent drug. Small amounts of this metabolite were also

detected in Study MB 102003, in which only 2.5% of the administered dose was recovered in the urine as unchanged dapagliflozin.

Consequences of possible genetic polymorphism

In order to study the effects of UGT1A9 single-nucleotide polymorphisms (SNPs) on estimated dapagliflozin clearance, pharmacogenetic analysis was conducted to explore the association between estimated dapagliflozin clearance and SNP genotypes from the UGT1A9 gene for subjects participating in Study MB102008 (pharmacogenetic report). Statistical analysis of the clearance values for the eight SNPs identified was undertaken. Effect ratios for the SNPs were in the range 0.79-1.3 and their 95% CI did not cross unity. Given that UGT1A9 controls the major metabolic pathway for dapagliflozin, potential for genetically determined variations in PK properties appears to be low.

Dose proportionality

Linear dose proportionality was established across the wide dose range of 2.5-500 mg in Study MB 102001. Single oral doses were given using combinations of 10 mg and 100 mg capsules and for lower doses the 0.5 mg/mL solution. Proportionality was more exact as assessed by AUC, particularly in the range of doses up to 50 mg. In multiple dose Study MB 102002 in which the dose range was 2.5-100 mg daily with escalation in the ratio 1:4:8:20:40, the ratios for geometric mean for dapagliflozin $AUC_{(TAU)}$ in the relevant dosage groups were 1:4:7:21:44 on Day 1, 1:4:7:19:40 on Day 7, and 1:4:7:20:44 on Day 14.

Dose proportionality was similarly observed with 5, 25 and 100 mg doses in a study of T2DM subjects half of whom were on metformin (MB 102003).

As noted previously, there is a remarkable consistency of dose related drug exposure, with AUC values conforming closely to a ratio of approximately 50 ng.h/mL/mg administered dose across the entire dose range tested. The wide range of doses tested reflects some uncertainty on the part of the sponsors as to what would be the eventual therapeutic dose; it is clear from the earlier studies that the original expectation was for a dose requirement of 20-50 mg, compared with the 5-10 mg eventually determined.

Time dependency

The absolute PK measurements undertaken in Study MB 102002, referred to above, showed some evidence of accumulation of dapagliflozin at higher dose levels during 14 days of daily oral administration. With 100 mg daily dosage, the mean C_{max} increased by 15% and the AUC by 12% between Day 7 and Day 14. At doses of 10 mg and below, however, there were no such changes and steady state appeared to have been reached by Day 7. Data included in the population pharmacokinetic analysis (PPK) show that these exposure data remain unchanged at intervals up to 24 weeks of administration.

Intra and inter individual variability

There is no dedicated study or specific data available on intra-individual variability. The best estimates available are firstly the coefficients of variation (CV) of the data in the PK studies in the application, which essentially yield a combined measurement of intra and inter individual variability, as well as analytical variation; and secondly the data from the population modelling exercise undertaken by the sponsor shown in the table reproduced below. The latter is a "worst-case scenario", in that it combines data from a wide range of sources including different dose levels; it enables calculation of CV values, for example, of 19.4% for steady state exposure in the age reference group and 17.3% of the White population. Data from individual studies evaluated in this report show that the CV for AUC measurement of dapagliflozin are mostly in the range 15-25%. An exception was Study MB 102057 in which much higher variances were reported not only for dapagliflozin but of even greater magnitude for the comparator drug bumetanide. It was also evident in Study

MB 102036 that the variability of the PK data for dapagliflozin was less than that of the comparator drug valsartan. In summary, the evidence available to this evaluation shows no evidence of excessive or unacceptable variability in the pharmacokinetic characteristics of dapagliflozin.

Pharmacokinetics in the target population

The sponsor provided two reports: firstly an exploratory modelling and simulation exercise undertaken in February 2008. This employed pooled plasma concentration-time data from Studies MB102003 and MB102008 in association with mathematical modelling and informed the selection of doses in the range 2.5-10 mg in subsequent Phase III studies. Secondly there is a population pharmacokinetic (PPK) report produced in October 2010. The PPK analysis extended the exploratory exercise, based on 8011 samples from 30 healthy subjects and 1223 subjects with T2DM sourced from five of the studies reviewed in this report: MB102002, MB102003, MB102013, MB102032, and D1690C00006. The modelling exercise combines information on exposure (PK data) and response (efficacy data) at the widely varying dosage levels used in the development program to produce predictions of exposure and response at the 10 mg dapagliflozin dose used in the later Phase III studies and now proposed for marketing. These exposure-response predictions are commented upon in subsequent sections of this report relating to efficacy and safety. The PPK data are also useful to this report in the sense of providing information on PK exposure in various subpopulations which formed covariates in the mathematical model, as shown below in Table 4.

Table 4. PPK data on PK exposure in various subpopulations

COVARIATE	Number of Subjects	Median AUCss (ng.hr/mL)			Median relative to Subgroup Reference (%)
		Median	5th Percentile	95th Percentile	
Age					
40≤Age<65 years[a]	924	444	274	803	
Age>=65 years	224	568	348	970	128
Age<40 years	105	402	252	639	90.1
Body Weight					
75≤BWT<100 kg[a]	614	459	295	832	
BWT<50 kg	4	727	464	1030	158
BWT>=120 kg	91	353	243	676	76.9
Renal Function					
Mild	692	471	292	843	117
Moderate	135	606	373	1000	151
Normal[a]	426	401	254	703	
Gender					
Female	619	507	314	911	124
Male[a]	634	413	260	722	
Race					
Asian	47	443	296	987	96.9
Black	43	475	275	628	104
White[a]	1147	457	277	854	

[a]Subgroup reference in each covariate category.

The variance in the data implied by the 5th and 95th percentile estimates, which can be recalculated as CV values in the 15-20% range, have already been commented upon above. With regard to the right-hand column indicating the median predicted PK exposure relating to the variables on the left, there are two obvious outliers: low body weight, and moderately impaired renal function. The prediction on low body weight is based on a very small number of observations (total 4) and, as the report acknowledges, is not a valid conclusion. The prediction on renal function is commented upon below and is consistent

with other data in the application (Study MB102007). Otherwise, the predicted median exposures are encompassed between 77-128% of the reference group in each category.

PK data acquired during the 24 week double blind short term period of some of the efficacy studies reviewed under *Efficacy* were included in the PPK analysis and show that dapagliflozin exposure characteristics (AUC) remain unchanged at intervals up to 24 weeks.

Pharmacokinetics in special populations

Children

No data were submitted, although it is noted that there is a paediatric development plan and that studies in this population are currently in progress (see comment under *Efficacy*).

Elderly

No dedicated study was undertaken. The PPK data in the Table 4 predict 28% greater exposure for the age group 65 years and over by comparison with the 40-65 age group. The sponsor has not felt this to be sufficient evidence for an age-specific dose recommendation, which is reasonable in view of the pharmacodynamic dose response and dose related tolerance characteristics of dapagliflozin. However, the possibility of a greater variation existing for older age groups in the 70-80 year range has not been examined or excluded.

Gender

The PPK analysis suggests that there is no gender effect on PK characteristics of dapagliflozin.

Weight

The PPK data suggest a small inverse correlation between dose related exposure and body weight, which might be expected on theoretical grounds. The apparent large increase for very low body weight subjects is not a valid observation in view of the small number of subjects assessed. Overall, the data do not suggest the need for a weight related dose adjustment.

Race

Most of the submitted pharmacokinetic studies, performed in the USA, were carried out on study populations containing roughly equal proportions of Caucasian and African-American subjects. Qualitative perusal of these data does not show any obvious difference attributable to this ethnic factor.

Two studies (MB 102010 and MB 102025)- were carried out on Japanese subjects. In the former, in which the subjects were healthy males, values for C_{max} and AUC following single doses of dapagliflozin in the range 2.5-50 mg were closely similar in absolute terms to those found in the USA subjects of mixed ethnic background in the earlier studies referred to in the previous paragraph and maintained the same ratios of dosage proportionality as was found in those studies.

It appears unlikely that race or ethnicity has any effect on the PK characteristics of dapagliflozin.

Impaired renal function

Dapagliflozin exposure is significantly increased in the presence of impaired renal function. Study MB 102007 showed AUC for dapagliflozin to be increased after a 50 mg dose, by 28%, 52% and 75% in type 2 diabetic subjects with 3 grades of progressively more severe renal dysfunction. These grades of renal dysfunction were classified mild, moderate and severe according to thresholds of creatinine clearance (CrCl) as estimated

by the Cockcroft-Gault calculation. The maximum CrCl for moderate classification, in whom exposure was increased 52%, was 50 mL/min. Exposure for dapagliflozin 3-O-glucuronide was increased more markedly by 50%, 101% and 154% in the three groups. Similar findings applied after 7 days of 20 mg dosage. Despite the increased exposure, the glucuretic response to dapagliflozin was progressively less with each further impairment of renal function, consistent with this pharmacodynamic response being rate limited by the filtered load of glucose as determined by the glomerular filtration rate.

The finding of increased drug exposure with impairment of renal function was confirmed by the PPK analysis as shown in the Table 4 above.

Impaired hepatic function

The effect of impaired hepatic function on the PK properties of dapagliflozin was the subject of a dedicated study, MB102027, undertaken in non diabetic subjects with liver disease by comparison with healthy subjects. The liver disease was characterised according to the modified Child-Pugh classification of the severity of liver disease.[33] This takes into account the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time and the degree of encephalopathy. A total score of 5-6 is considered Grade A (well compensated disease); 7-9 is Grade B (significant functional compromise); and 10-15 is Grade C (decompensated disease). These grades correlate with one and two year patient survival of, for Grade A: 100% and 85%; Grade B: 80% and 60%; and Grade C: 45% and 35%.

The data for the Class B and C subjects shows an increase in dapagliflozin exposure both in terms of C_{max} and AUC, the latter ($AUC_{0\text{-}inf}$) being increased above the healthy subject value by 36% in Class B and 67% in Class C subjects.[34]

Although the above conclusions from the data of Study MB 102027 appear robust, some of its findings in relation to the relative concentrations of parent drug and metabolite are difficult to reconcile with the presumed explanation of reduction in the hepatic component of conversion to dapagliflozin-3-O-glucuronide. They do not, however, affect the conclusion that dapagliflozin exposure is increased by up to two thirds in subjects with more severe grades of liver disease but not in those with mild (Child-Pugh Class A) disease.

Evaluator's overall comments on pharmacokinetics in special populations

The sponsor has carried out a comprehensive program of evaluation of the PK of dapagliflozin in various subpopulations in which the drug is likely to be used. There is no evidence of clinically significant variation of the PK properties in any of the subpopulations described above, with the exception of those with impaired renal or hepatic function. The finding in relation to renal function is of diminished importance in the sense that a degree of renal dysfunction which causes retention of the drug also significantly impairs its pharmacodynamic response, as described below. The finding in relation to impaired hepatic function was commented upon further relating to the draft product information (PI).

Pharmacokinetic interactions with other medicinal products or substances

In vitro pharmacokinetic interactions

Not examined in this evaluation.

[33]Surgery and portal hypertension. Child III, CG, Turcotte, JG. In: The Liver and Portal Hypertension, Child III CG (Ed), Saunders, Philadelphia 1964. p.50

[34] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

In vivo pharmacokinetic interactions

A number of drug-drug interaction studies, mostly using single doses, have been conducted to evaluate the consequences of co administration of dapagliflozin with other oral antidiabetic agents, with cardiovascular medications which are frequently taken by patients with T2DM, and with rifampicin as an indicative CYP 450 enzyme inducer.

Studies with other oral antidiabetic agents

The oral agents studied in conjunction with dapagliflozin in the interaction studies reviewed in this section include the biguanide metformin, a sulphonylurea, a DPP4 inhibitor, a thiazolidinedione and an alpha glucosidase inhibitor. These drug classes comprise all the currently available therapeutic options for T2DM, apart from insulin.

The diabetes medication most likely be used in conjunction with dapagliflozin is metformin. Study MB 102026 shows that dapagliflozin in 20 mg dosage has no effect on the PK of metformin and neither does metformin (1000 mg) affect the PK of dapagliflozin.

Study MB 102037 assessed possible PK interaction between dapagliflozin and glimepiride (a sulphonylurea) and sitagliptin (a DPP4 inhibitor). Neither drug showed any effect on the PK of dapagliflozin. Dapagliflozin had no effect on the PK of sitagliptin. When co administered with dapagliflozin 20 mg, glimepiride at 4 mg dosage showed increased exposure as assessed by AUC parameters of approximately 12%. This is not felt to be clinically significant.

PK interaction of dapagliflozin with pioglitazone, a thiazolidinedione, was examined in Study MB 102017. No effect of either drug on the PK properties of the other was demonstrated. In this study, the PK properties of the major metabolite of each drug (hydroxy-pioglitazone and dapagliflozin 3-O-glucuronide) were also examined, as described above, and were also found free from any effect attributable to drug-drug interaction.

Potential interaction with voglibose, a member of the class of alpha glucosidase inhibitor (AGI) drugs, was examined in Study D1692C00002. As a class, AGI undergo very little absorption or metabolism and act within the gut lumen. Any drug-drug interaction would therefore only be likely to occur either as a consequence of a direct *in vitro* type reaction with the other drug concerned or as an atypical food effect due to an increase in the quantity of undigested carbohydrate substances present in the gut lumen. No evidence of any effect of voglibose on the PK of dapagliflozin was found in Study D1692C00002.

Unlike the other antidiabetic agents used in the studies in the section (metformin, glimepiride, pioglitazone and sitagliptin), voglibose is not used in Australia where the only AGI registered for the treatment of T2DM is acarbose. Particularly in view of the possible mechanisms of interaction outlined in the previous paragraph, it is likely but obviously not certain that these findings would apply to use of dapagliflozin with acarbose. It is noted that reference to voglibose has been deleted in the drug interaction section of the proposed PI.

Studies with cardiovascular and related medications

A lack of effect of hydrochlorothiazide on the PK of dapagliflozin and vice versa was shown in Study MB 102004.

The loop diuretic bumetanide was examined for possible PK interaction in Study MB 102057. Bumetanide is structurally different from frusemide, the loop diuretic more commonly used in Australia; frusemide, like the thiazides, is a derivative of sulphanilamide. The results of Study MB 102057 are uncertain due to a small number of subjects (14) in the control group given dapagliflozin alone and an unusually high degree of variance in some of the study parameters. The effect of dapagliflozin on the PK of bumetanide failed the "no effect" criterion of 90% CI for the ratio of treatment effects

being within 0.80-1.25. The authors report a 13% increase in exposure (AUC) for bumetanide when co administered and an 8% increase for dapagliflozin, using a statistical model which results in adjustments to the mean baseline value. Calculating the interaction effect simply using the within group AUC values, however, yields an estimation of the increase in exposure for bumetanide at 28%, and for dapagliflozin 19%, when coadministered. The confidence in any of these estimations is low and they may simply be due to random statistical variation particularly as related studies in the application shown little propensity of dapagliflozin for interaction of this nature. Even at the worst case quoted values, the effect would be unlikely to be of clinical significance.

PK properties of the angiotensin II receptor blocker valsartan, while showing an intrinsic wide variability, appeared unaffected by co administration with dapagliflozin and the PK of dapagliflozin were not affected by valsartan (Study MB 102036).

Dapagliflozin PK were not affected by co administration with simvastatin but in combination with dapagliflozin 20 mg, simvastatin at 40 mg dosage exhibited approximately 20% increase in exposure (Study MB 102036). The sponsor has not suggested that this is clinically significant or deserving of any cautionary advice and this is felt to be reasonable in light of the fact that this drug undergoes dosage titration in clinical practice by progressive 100% increments.

Study MB 102058 examined the potential for PK interactions with warfarin and digoxin. No influence of either drug on the PK of dapagliflozin or vice versa was demonstrated. The warfarin protocol included measurement of the more active enantiomer S-warfarin and its opposite R-warfarin and there were no changes in the quantities or ratio of the two substances.

Studies with inhibitors or inducers of CYP 450 enzymes

The effect of rifampicin, a potent inducer of a number of CYP450 enzyme systems, on the PK of dapagliflozin was evaluated in Study MB 102074. As dapagliflozin is suggested by the sponsor not to be a substrate for CYP450 but to be principally metabolised to dapagliflozin 3-O-glucuronide through enzyme UGT1A9, a "no effect" result might have been anticipated; however, a 22% reduction in dapagliflozin exposure (AUC parameters) was observed. The study authors suggest this to represent induction by rifampicin of UGT1A9 but admit, although there is some confusion in the discussion, that their data is not completely consistent with this explanation particularly as the proportion of the glucuronide metabolite recovered in urine was decreased rather than increased as might have been expected. Furthermore, the clinical evaluator was not been able to locate evidence that rifampicin does induce UGT1A9 beyond the reference produced by the authors[35] which only refers to it as a possible action. The explanation remains unclear but is not a matter of practical importance as the pharmacodynamic effect of dapagliflozin (urinary glucose excretion) was reduced only by 10% which would not be clinically significant.

There are no specific studies of interaction with CYP 450 antagonists.

Potential effect on renal excretion of other drugs

Dapagliflozin's mechanism and site of action raises the possibility of unexpected effects on the pharmacokinetics of renally excreted drugs, particularly those whose mechanism of elimination involves the renal tubule. The drug interaction studies included in the application which focused on drugs likely to be co administered with dapagliflozin do not specifically address this question but do contain relevant data. Sitagliptin is excreted

[35]Kuypers DR, Verleden G, Naesens M, et al (2005). Drug interaction between mycophenolate mofetil and rifampin: possible induction of uridine diphosphate-glucuronosyltransferase. Clin Pharmacol Ther 78(1):81-8

principally by a renal mechanism involving active tubular secretion[36]; in co administration with dapagliflozin its C_{max} was slightly reduced but total exposure remained unchanged (Study MB 102037). The PK of digoxin, also eliminated by active renal tubular secretion[36], was likewise unchanged in coadministration with dapagliflozin (Study MB 102058). Amongst the other drugs examined in the included studies, metformin, hydrochlorothiazide, and bumetanide all undergo predominantly renal excretion[36] and their PK was not affected in co administration with dapagliflozin, although in these cases the elimination mechanisms are dependent on glomerular filtration rather than tubular function.

Evaluator's overall comments on pharmacokinetic interactions

Dapagliflozin appears free from interference with its PK by drugs with which it is likely to be co administered and to be free from any tendency to in turn affect the PK of such other drugs. The sponsor's explanation that this desirable property is attributable to the mechanism of dapagliflozin's major clearance mechanism being catalysed by UGT1A9 rather than the CYP450 system appears sound. The lack of effect on the PK of those renally excreted drugs tested is reassuring but vigilance will need to be maintained for the possibility of interaction effects with drugs eliminated by specific renal tubular mechanisms.

Dapagliflozin may have an adverse effect on renal function, particularly when there is pre-existing impairment (see Safety below); it is noted that there are no interaction studies with potentially nephrotoxic drugs, particularly Non Steroidal Anti Inflammatory Drugs (NSAID).

Exposure relevant for safety evaluation

The sponsor's summary states that 688 subjects participated in the 26 studies summarised in the section and that 635 of these were exposed to dapagliflozin. Of these, 632 were accounted for by this evaluation; the discrepancy is due to a small number of subjects treated in studies which were prematurely discontinued and not reported. Of those treated, 222 received single doses, some quite large; three groups of 6 subjects received doses of 100, 250 and 500 mg respectively. Some 102 subjects were treated for 14 days with daily doses mostly in the 5-20 mg range but as high as 100 mg (22 subjects). Some 180 subjects received single or multiple doses at the 10 mg level proposed for marketing.

Evaluator's overall conclusions on pharmacokinetics

The PK characteristics of dapagliflozin have been adequately characterised by the program of studies undertaken by the sponsor. Absorption following oral administration is rapid, with T_{max} usually within one hour and relatively unaffected by food ingestion, as is overall exposure. Dose proportionality is shown to be consistent over a remarkably wide dosage span well exceeding the likely therapeutic range. Metabolic clearance and excretory mechanisms have been well defined, the major pathway being via hepatic and renal conversion to the inactive metabolite dapagliflozin 3-O-glucuronide which is excreted renally. Consistent with this, moderate or severe impairment of hepatic or renal function gives rise to increased drug exposure.

The sponsor has conducted a comprehensive program of pharmacokinetic interaction studies with drugs which are most likely to be co administered with dapagliflozin and these have revealed no evidence of significant interference by these drugs with

[36] Australian approved product information, Phoenix medical publishing, May 2011

dapagliflozin pharmacokinetics such as to necessitate any recommendations regarding dosage adjustment.

The apparent small increase (12%) in exposure of glimepiride when coadministered with dapagliflozin is not felt to be clinically significant or require a recommendation regarding dosage adjustment.

In general, the PK characteristics of dapagliflozin are stable, relatively free from interference by subject characteristics or external factors and not prone to interaction with co administered drugs.

Pharmacodynamics

Introduction

The drugs primary biological action is inhibition of tubular reabsorption leading to increased urinary excretion of glucose and sodium. Important consequent actions can include an effect on water balance and on the renal tubular handling of other substances, particularly calcium, the urinary excretion of which may parallel that of sodium under some circumstances.

Mechanism of action

The primary pharmacodynamic action of dapagliflozin is to inhibit SGLT2 and thereby increase the urinary excretion of glucose (glucuresis, glucuretic effect). Under physiological conditions, with normal blood glucose, the Tm of SGLT2 is sufficient for reabsorption of the entire renal tubular filtered load of glucose so that glycosuria does not occur. The amount of glucuresis, which is glycosuria pharmacologically promoted in this case by dapagliflozin, will be determined by the degree of inhibition of SGLT2 and the quantum of the filtered load of glucose. In turn, it will therefore depend on three factors: the blood glucose level, the glomerular filtration rate, and the effective dose of dapagliflozin.

Primary pharmacodynamics

The threshold for the glucuretic action of dapagliflozin was established in low dose Study MB 102088. In these healthy young adults, the lowest dose at which glycosuria appeared was 0.3 mg; at this level mean 24 hour urinary glucose excretion was 538 mg, a physiologically insignificant amount. With higher doses, quantitatively significant amounts appeared; 19.1 g/24 h at 1 mg daily and 22.9 g/24h at 2.5 mg daily. At these doses, renal tubular glucose reabsorption was 21% and 25% inhibited, respectively, whereas it was <1% inhibited at the 0.3 mg dosage.

In Study MB 102025 a dose range of dapagliflozin encompassing that now proposed for marketing was used over a 14 day period in Japanese subjects with T2DM. Total daily glucose excretion close to 40 g over 24 h was seen with the 2.5 mg dose, 70 g with 10 mg with 75 g after the 20 mg dose, with little variation between Day 1 and Day 14. Timed urine collections showed that urinary glucose excretion reached its peak between 8 and 12 h after dapagliflozin administration. There was a dose dependent increase in glucose clearance, resulting from inhibition of tubular reabsorption of glucose, which was slightly greater in the first 4 h than in the second 4 h after dapagliflozin administration. The dose dependency demonstrated in the study was mainly between 0, 2.5 and 10 mg dapagliflozin with little increase between 10 and 20 mg.

In Study MB 102008, dapagliflozin 10 mg daily given to T2DM subjects for 12 weeks resulted in mean urinary glucose excretion of 68 g/24h. In the earlier Study MB 102003 in

which T2DM subjects were given higher doses for 14 days, glucose excretion was approximately 80 g at 25 mg and 120 g at 100 mg dapagliflozin daily. At these higher dosage levels, tubular glucose reabsorption was 33-44% inhibited compared with 19-20% at 5 mg daily. Similar data was obtained in healthy subjects in Study MB 102002; at the proposed marketing dose of 10 mg dapagliflozin, % inhibition of glucose reabsorption was in the range 35-60% and the 24 h glucose excretion approximately 35 g (no summary statistics provided), whereas with the higher doses of 20-100 mg dapagliflozin, glucose reabsorption was inhibited 45-75%.

Study MB 102001 in which single oral doses of up to 500 mg were administered, the results showed some dose proportionality of urinary glucose excretion up to the 20 mg dose level but it did not increase further with higher doses.

In summary, the minimum effective daily dose of dapagliflozin is 1 mg and the maximum probably 20 mg. The proposed dose of 10 mg gives a near maximal response of glucuresis at approximately 60 g/24 h; as pointed out in the sponsor's *Summary of Clinical Pharmacology*, this represents a significant loss of caloric energy approximating 225 kilo calories (kcal; 160 kilo Joules (kJ)).

The effect of moderately impaired renal function (CrCl 30-59) on the pharmacodynamic response to dapagliflozin was assessed in Study MB 102029. In these diabetic subjects at Week 6, the 24 hour glucose excretion was 31.2 g/24 h for the 5 mg dosage group and 32.6 g/24 h for the 10 mg group. These figures appear significantly less than those found at these dosages in T2DM subjects with normal renal function. Consistent with this finding, efficacy of dapagliflozin in reducing blood glucose was reduced in this study population.

Study MB 102007provides further evidence that the glucuretic action of dapagliflozin is progressively impaired with diminishing renal function.

A study was planned (MB 102020) to examine the possibility that the dapagliflozin kinetics of renal glucose reabsorption might differ between diabetic and healthy subjects. This was abandoned after enrolment of one subject due to "serious non-compliance" on the part of the study investigator, who is a person of some eminence in American diabetology. The sponsor's *Clinical Overview* indicates that a further study on the subject is in progress. It would seem that if there is a difference of this nature, it would reflect itself in the outcomes of the efficacy studies which can be judged on their own merits. While the subject is of some scientific and academic interest, it would not appear essential to the findings of this evaluation report.

Secondary pharmacodynamics

Secondary actions of dapagliflozin include natriuresis, an associated calciuresis and an uricosuric effect.

The natriuretic and calciuretic effects were evaluated in some detail in Study MB 102057. In common with bumetanide (and other loop diuretics), dapagliflozin promotes urinary loss of both sodium and calcium. The study found that the action of dapagliflozin in promoting urinary sodium and calcium loss is less than that of bumetanide and in co administration, it does not enhance those effects of bumetanide. Whereas bumetanide alone or dapagliflozin in combination with bumetanide both gave rise to a physiological compensatory rise in plasma renin, this did not occur with dapagliflozin given alone which suggests that the natriuretic effect of dapagliflozin, which is transient, is at least in most subjects not physiologically significant.

In the early Phase I single dose Study MB 102001 there was also some evidence of increased urinary calcium excretion in the first 48 h after dosing. This was not confirmed in the multiple dose Study MB 102002, although some subjects showed elevations of parathyroid hormone (PTH). However, inspection of this data suggested that these PTH

changes might be attributable to a vitamin D deficiency rather than a response to any calciuretic action of dapagliflozin. An increase in the 24 h urinary calcium was also found on the first day of dapagliflozin administration to Japanese T2DM subjects in Study MB 102025 but it did not persist after 14 days of administration and furthermore was equally evident in subjects given placebo as in the various dapagliflozin dosage groups. In this study as well as in Study MB 102001, it seems most likely that the increase in calcium excretion early in the study reflects the change in calcium intake on commencing the study diet, which was supplemented the calcium. None of the studies had a sufficient run-in period to ensure stable calcium balance.

In summary**,** it is possible that dapagliflozin causes a mild, sustained increase in urinary calcium excretion but this can neither be confirmed nor excluded with the available data.

Resulting from the glucuresis and probably to some extent the associated natriuresis, there is a mild osmotic diuresis; in Study MB 102008 a sustained increase in urinary volume approximating 375 mL daily was documented after 12 weeks treatment. This is presumed to be the explanation for the occasional occurrence of hypovolaemic episodes and possibly also the sustained increase of approximately 2% in haematocrit seen in dapagliflozin treated subjects, as discussed under *Safety*.

A further outcome of the renal tubular action of dapagliflozin is an increase in uric acid excretion (uricosuric effect): in Study MB 10205, urinary uric acid excretion rose markedly, albeit transiently, in response to dapagliflozin, resulting in a *reduction in serum uric acid* from Day 1 to Day 8 of 1.94±0.73 mg/dL, a fall of 35% from the baseline value.

Relationship between plasma concentration and effect

There are no data directly relating PK to PD response measured by glucuretic effect. However, the PPK report includes an exposure-response analysis for efficacy as reflected by changes in glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG). This was conducted with data from 742 subjects with drug naïve T2DM collected up to Week 24, before the use of any rescue medication, during the short term treatment phase in two Phase III monotherapy studies (MB102013, MB102032). This analysis predicts that a 10 mg daily dose will achieve 74.7% of the theoretical maximum effect of dapagliflozin on FPG and HbA1c (5th, 95th percentiles of prediction: 52.6%, 89.5%).

Pharmacodynamic interactions with other medicinal products or substances

The major secondary pharmacodynamic action of dapagliflozin is to increase urinary sodium excretion. This natriuretic action is shared by diuretics which are commonly used in the management of Type 2 diabetes and its complications, including thiazides either alone or in fixed combination products, and loop diuretics. Pharmacodynamic interaction with the loop diuretic bumetanide was examined in Study MB 102057 and has already been referred to above. In common with bumetanide (and other loop diuretics), dapagliflozin promotes urinary calcium as well as sodium loss. The study found that the action of dapagliflozin in promoting urinary sodium and calcium loss is less than that of bumetanide and in co administration, it does not enhance those effects of bumetanide.

The interaction between dapagliflozin and hydrochlorothiazide (HCTZ) in terms of urinary sodium excretion was examined in Study MB 102004, although in less detail as this was only a single dose protocol. Following administration of HCTZ alone, urinary sodium excretion rose from baseline by approximately 60 mEq/24 h. After 50 mg dapagliflozin, this rise approximated 32 mEq/24 h. Following co administration of the two treatments, the rise in urinary sodium excretion was approximately 126 mEq/24 h, suggesting a possibly synergistic but at least additive effect of the two treatments on this parameter. Urinary calcium was not measured in this study but would be of less concern as the action of thiazides is to reduce urinary calcium.

A number of medications may have a minor effect on the pharmacodynamic properties of dapagliflozin as a consequence of interaction with its pharmacokinetics. These have been described above and include a 10% reduction in urinary glucose excretion with rifampicin. Dapagliflozin's primary pharmacodynamic action of glucuresis may also be slightly impaired by coadministration with bumetanide, although the evidence is equivocal.

The PK interaction study with warfarin (MB 102058) included measurements of anticoagulant effect (international normalized ratio (INR)[37]) and these showed no change when warfarin was coadministered with dapagliflozin.

Genetic differences in pharmacodynamic response

This has not been specifically studied but given the negative results for the impact of SNPs of UGT1A9 on dapagliflozin PK (Study MB102008, pharmacogenetic report) and the generally close PK/PD relationship, an effect of this nature appears unlikely.

Evaluator's overall conclusions on pharmacodynamics

Dapagliflozin's primary PD action of glucuresis is well defined by the included studies and is of a physiologically significant degree predictive of efficacy in reducing blood glucose. The limits of the biologically effective dose range have been defined. Secondary pharmacodynamic actions include urinary sodium loss which is not of a degree which would be clinically significant unless diuretic agents are also being used. A diuretic effect is evident sufficient to be significant if other factors are present which might lead to volume depletion. There is an increase in urinary calcium excretion but whether this is sustained over the long term is uncertain. There is a sustained increase in urinary uric acid excretion, sufficient to reduce the serum uric acid level significantly.

Efficacy

Introduction

The 14 studies of efficacy and safety which comprise the sponsor's clinical development program are listed in Table 5 below. In this section, their efficacy findings are reviewed in relation to the various indications applied for in the application.

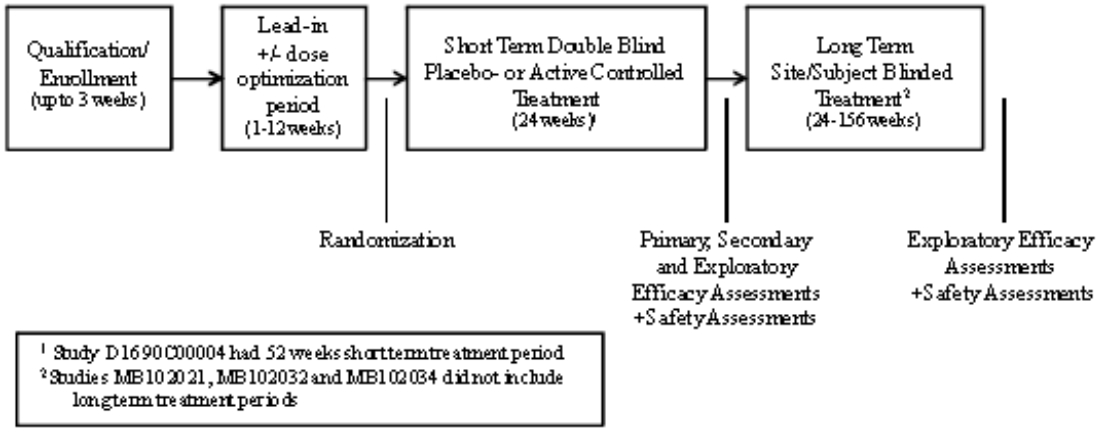
[37] The prothrombin time (PT) and its derived measures of prothrombin ratio (PR) and international normalized ratio (INR) are measures of the extrinsic pathway of coagulation. They are used to determine the clotting tendency of blood.

Table 5. Efficacy and Safety studies submitted with this application.

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin/Total
Phase 2b studies		
MB102008 12 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, 10, 20, and 50 mg, placebo and metformin XR 750/1500 mg 47-59/279/389
MB102009 12 weeks	Insulin-dependent subjects with HbA1c ≥7.5% and ≤10.0%	Dapa 10 or 20 mg and placebo 23-24/48/71
D1692C00005 12 weeks	Japanese subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, 5, and 10 mg and placebo 54-59/225/279
Phase 3 studies		
Monotherapy		
MB102013 24 plus 78 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0% Open treatment group with HbA1c ≥10.1% and ≤12.0%	Dapa 2.5, 5, and 10 mg and placebo 64-76/410/485 Dapa 5, 10 mg 34-39/73/73
MB102032 24 weeks	Drug-naive subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, and 5 mg and placebo 68-74/214/282
Add-on combination therapy with metformin		
MB102014 24 plus 78 weeks	Subjects on metformin ≥1500 mg/day with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 135-137/409/546
D1690C00012 24 plus 78 weeks	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥6.5% and ≤8.5%	Dapa 10 mg and placebo 91/91/182
Add-on combination therapy with insulin		
D1690C00006 24 plus 24 plus 56 weeks	Subjects on insulin ≥30 IU/day ± maximum 2 OAD with HbA1c ≥7.5% and ≤10.5%	Dapa 2.5, 5, and 10 mg and placebo 196-212/610/807
Add-on combination therapy with TZD		
MB102030 24 plus 24 weeks	Subjects on pioglitazone with HbA1c ≥7.0% and ≤10.5%	Dapa 5, and 10 mg and placebo 139-141/281/420
Add-on combination therapy with SU		
D1690C00005 24 plus 24 weeks	Subjects on SU with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596
Initial combination therapy with metformin		
MB102021 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 5 mg + metformin extended release (XR) up to 2000 mg, dapa 5 mg, and metformin XR up to 2000 mg 194-203/397/598
MB102034 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 10 mg + metformin XR up to 2000 mg, dapa 10 mg, and metformin XR up to 2000 mg 208-219/430/638
Active comparator		
D1690C00004 52 plus 156 weeks	Subjects on metformin >1500 mg/day with HbA1c >6.5% and ≤10.0% Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10 mg and glipizide titrated to 5, 10, and 20 mg 406-408/406/814
Special populations		
MB102029 24 plus 28 plus 52 weeks	Subjects with moderate renal impairment (GFR >30 to <60 mL/min/1.73m^2 on a stable anti-diabetic regimen with HbA1c ≥7% and ≤11%	Dapa 5 and 10 mg and placebo 83-85/168/252

The 3 Phase IIb studies and 11 Phase III studies shown in the table included 6436 randomised and treated subjects with T2DM, of whom 4495 were treated with dapagliflozin at doses ranging from 1 mg to 50 mg. The Phase IIb studies will be included in the general discussion of efficacy data as, with the single exception that the period of double blind treatment for assessment of the primary efficacy parameter was 12 rather than 24 weeks they share a similar protocol with the Phase III studies. Each contains a double blind treatment period, contains a group treated with the 10 mg dose chosen for evaluation in the Phase III program and one was conducted after the Phase III program had started. The protocol for the Phase III studies had the general structure shown below (Figure 3; sponsor's *Summary of Clinical Efficacy*).

Figure 3. Protocol for the Phase III studies



The following procedures and criteria were common to all the studies:

The primary efficacy parameter was change in HbA1c, relative to placebo or active control as appropriate, from baseline to the end of the 24 week short term treatment period. There were two exceptions; Study D1690C00004, in which there was a 52 week treatment period, and Study D1690C000012 in which the primary efficacy parameter was change in body weight. The Phase IIb studies with their 12 week treatment period are for the purposes of this report included as supporting evidence together with the Phase III studies. Twelve weeks is recognised as the minimum time for evaluation of change in HbA1c and in the Phase III studies change in HbA1c was generally evident by 12 weeks with little if any further change by 24 weeks.

Secondary outcome measures assessed at the end of double blind treatment in all studies included change in fasting plasma glucose (FPG); change in body weight or BMI, and sometimes waist circumference; and the proportion of subjects achieving predefined HbA1c targets, usually ≤7%. In several studies, the effect of dapagliflozin on post prandial glucose control was assessed by measuring the change from baseline in plasma glucose following a glucose challenge. Several studies also assessed change in HbA1c and subgroups defined by body weight (mostly BMI ≥27) or higher baseline HbA1c (usually ≥9%).

Recruitment of T2DM subjects by study centres was undertaken without reference to age or gender, except for a general lower age limit of 18 years and an upper limit of 77 years when metformin was part of the protocol; the demographics of the study populations reflect those of T2DM, with quite even gender balance (except for Japanese study D1692C00005, which reflects cultural factors) and most subjects in the age range 40-65, so that the mean age of study populations was in the range 52-59 years. Subjects were required to have inadequate glycaemic control, defined as HbA1c >7% (sometimes >7.5%) with an upper limit imposed for most studies of 10-10.5%.

Inclusion and exclusion criteria were appropriate and as expected for the types of study involved, were applied uniformly to the various studies and need not be described in detail in this report. A specific exclusion based on the mechanism of action of dapagliflozin was the presence of severe renal impairment, defined as eGFR[38] <30 mL/min/1.73 m^2.

Other diabetes medications: for the monotherapy studies in particular, *drug naïve* subjects were recruited, defined as either never having received diabetes medication or having had such for <24 weeks since the diagnosis of diabetes, not for more than 14 days during 12 weeks prior to enrolment and not at all during the 4 weeks prior to enrolment. Otherwise, subjects were recruited with a medication history suitable to the specific protocol.

Randomisation: at each site, enrolled and consented subjects were allocated to a treatment group by means of designated study personnel accessing an interactive voice response system (IVRS) managed by the central study organisation, which would allocate a 5 digit code identifying the subject for the remainder of the study and determine double blind treatment allocation.

Blinding was achieved with the use of matching placebo tablets, including double dummy and triple dummy arrangements in the more complex protocols.

Rescue medication was given to subjects who failed to meet prespecified glycaemic targets. This varied from study to study but could include metformin, pioglitazone, rosiglitazone, sitagliptin, acarbose, or sulphonylureas.

Statistical analysis: in all cases, outcome data were calculated after exclusion of subjects who had received rescue therapy and for subjects who had discontinued for other reasons, on the basis of the last observation carried forward (LOCF).[39] Efficacy assessments were carried out on a data set consisting of all randomised subjects who had taken at least one dose of double blind medication. In those studies which were BMS sponsored (the majority), this is referred to as the Randomised Subjects Data Set and in the AZ sponsored studies the Full Analysis Set; which has an additional requirement of a non missing baseline efficacy value and at least one post baseline efficacy value. Some assessments are specified as being carried out on a per protocol population, excluding data affected by protocol deviations and documented prior to study unblinding. Statistical significance of the primary efficacy endpoint and all secondary outcomes based on continuous measurements was assessed using an analysis of covariance (ANCOVA) model, including the treatment group as a fixed effect and baseline value as a continuous covariate. In some studies, randomisation was stratified usually by category of pre enrolment medication, in which case this was included as an additional factor in the model. To control type 1 error rate, statistical testing of secondary endpoints was only carried out if the primary endpoint achieved significance and then in a sequential fashion with a predetermined hierarchical order of endpoints which was stopped at the point when one did not achieve significance.

Dose response studies

There is no dedicated study of dose responsiveness based on an efficacy (glycaemic) endpoint. This appears to reflect the fact that by the start of the Phase III program in 2007, the sponsor had considerable data from PD studies conducted as early as 2004 (see above) which could inform a choice of 10 mg as a likely effective therapeutic dose with near maximal efficacy on the mechanism (inhibition of renal tubular glucose reabsorption)

[38] The GFR (glomerular filtration rate) is the volume of fluid filtered from the renal glomerular capillaries into Bowman's capsule per unit time and it is the most accurate indicator of glomerular function. The "eGFR" is an estimated value derived from a measured serum creatinine and population means for age and gender.
[39] Sponsor comment; " In all cases, for the short term efficacy data were calculated after exclusion of data after the rescue for subjects who had received rescue therapy, on the basis of the last observation carried forward (LOCF)."

which would determine glycaemic response. Nevertheless, several Phase IIb/III studies provide evidence on dose responsiveness, as follows:

Study D1692C00005: a placebo controlled parallel group study of Japanese T2DM subjects, the mean reduction in HbA1c from baseline in the 1, 2.5, 5 and 10 mg dapagliflozin groups was 0.12%, 0.10%, 0.37%, and 0.44% respectively, compared with a rise of 0.35% in the placebo group. FPG also fell in all dapagliflozin groups in a dose related fashion, maximal for the 10 mg dose in which the fall was 32 mg/dL (1.8 mmol/L) compared with 9.5 mg/dL (0.5 mmol/L) for placebo. Improvement in AUC of serum glucose after a glucose load also showed a dose related trend, falling at Week 12 by 4992, 7570, 7266 and 8484 mg.min/dL in the 1, 2.5, 5 and 10 mg dapagliflozin groups, respectively.

Monotherapy Study MB 102013: mean reduction in HbA1c at 24 weeks was 0.23% with placebo and 0.58%, 0.76 % and 0.89% in the 2.5, 5 and 10 mg dapagliflozin groups respectively. Similarly, in Study MB 102014, the placebo adjusted mean reduction from baseline HbA1c was 0.38%, 0.41% and 0.54% at the 2.5, 5 and 10 mg dosage levels. In both these studies, parallel dose related reductions of FPG were also seen. At lower dose levels of 1, 2.5 and 5 mg used in Study MB 102032 (appendix 9.2.13), a dose related fall in HbA1c from baseline was seen of 0.68%, 0.72% and 0*.82% respectively* and dose related changes in FPG and 2 h post challenge glucose were also seen. Similar trends are evident in Study D1690C00006, in which dapagliflozin 2.5, 5 and 10 mg was given with insulin and in Study D1690C00005 in which the same doses were given with glimepiride.

In all of the above studies, the changes for each dapagliflozin group by comparison with placebo are statistically significant but there was no statistical testing of the dose related trend. This trend is nevertheless very consistent across the studies, sufficient to confirm that 10 mg dapagliflozin is more effective than lower doses. The only glycaemic evidence relating to doses above 10 mg is in Phase IIb studies MB 102008 and 102009; in the former, daily doses from 2.5-50 mg were used as monotherapy for 12 weeks. Significant reductions in HbA1c were seen with all doses but with no clear dose related trend. The 20 mg dose actually showed the least fall in HbA1c from baseline (0.55%); otherwise, the lowest fall was with 2.5 mg (0.71%) and the highest with 50 mg (0.90%). In Study MB 102009, dapagliflozin was given in 10 mg or 20 mg dosage daily for 12 weeks in the setting of failed treatment on other multiple therapies. HbA1c rose by 0.09% in the placebo group and fell by 0.61% with the 10 mg dosage and 0.69% with the 20 mg dosage.

The combination of the above findings provide strong supportive evidence of 10 mg daily being more effective than lower doses with little evidence to support increasing the dose to 20 mg or higher. This conclusion is consistent with the findings of the pharmacodynamic studies summarised above.

Main (pivotal) studies

Of the 11 Phase III studies, none stand out as having particularly more or less impact on the evaluation of the application in general. As will be noted from the Table 5, subject numbers are reasonably evenly spread between the studies and there are similar numbers of studies supporting the various indications (6 in number) applied for. In this report, the discussion and evaluation of the study findings are therefore related to the specific indication to which the study or studies relate and are arranged in the following sections in the same order in which the indications appear in the application. If any of the studies are pivotal, it is those supporting the indications of monotherapy and initial combination with metformin and these are discussed first.

Monotherapy

Study MB 102013, a major international study involving 485 subjects at 85 sites examined the efficacy of a variety of dapagliflozin regimens in treatment naïve subjects. Its dose related findings have already been referred to above. The placebo adjusted fall in HbA1c at

24 weeks was 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. FPG fell by a mean 1.4 mmol/L. Subjects with baseline HbA1c >9% did better, with HbA1c reductions approximating 2% but may represent a selected responder group. In a long term extension phase lasting 102 weeks, the majority of subjects discontinued progressively for lack of glycaemic control or need for rescue therapy. During the short term phase, versus placebo, body weight fell by approximately 1 kg more in the dapagliflozin subjects and 51% of subjects achieved HbA1c <7% compared with 32% in the placebo group.

Study MB 102032 showed similar findings, although the maximum dapagliflozin dose given was 5 mg. With this dose, HbA1c at 24 weeks fell by 0.82% compared with a rise of 0.02% in the placebo group. FPG fell by 1.58 mmol/L and body weight fell by 2.69 kg as compared with a fall of 0.96 kg in the placebo group. The 2 h post challenge plasma glucose level was reduced on average by 2.88 mmol/L compared with a rise of 0.49 mmol/L in the placebo group.

Supportive evidence is found in *Study MB 102008*, a 12 week Phase IIb trial which was placebo controlled and also had an active control arm using metformin monotherapy. For those treated with dapagliflozin 10 mg, HbA1c reduction at 12 weeks was 0.85% compared with 0.18% for placebo and 0.73*% for metformin*. The comparisons of metformin with placebo and metformin with dapagliflozin were not tested statistically but the difference between dapagliflozin 10 mg and placebo was highly significant. Fasting and post prandial glucose were also improved. Body weight decreased by approximately 3 kg (depending on the dosage group) as compared with a possible 1 kg in the placebo and 1.5 kg in the metformin groups.

A secondary outcome of Study MB 102034, discussed below, was the demonstration that dapagliflozin 10 mg monotherapy 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.

These data confirm efficacy of dapagliflozin 10 mg as monotherapy with a placebo controlled reduction in HbA1c of 0.6-0.7%, a clinically significant change. There is also evidence of improved control of both fasting and post prandial glucose and of weight loss greater than that achieved with metformin, with which dapagliflozin appears to have comparable glycaemic efficacy. Long term (2 year) duration of response was only shown for 25% of subjects.

Initial combination therapy with metformin

Support for this indication is found in 2 large (598 and 638 subjects respectively) trials; Studies MB 102021 and 102034 in which dapagliflozin in combination with metformin was compared with treatment arms in which the same two medications were given alone to treatment naïve subjects. In Study 102021, a 5 mg dose of dapagliflozin was used. Subjects 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 combination effect of 0.70% and 0.86% by comparison with the monotherapies was statistically significant. Comparable changes occurred in FPG. HbA1c <7% was achieved by 52.4% of combination therapy subjects compared with 22.5% and 34.6% for dapagliflozin or metformin monotherapy respectively. Combination therapy resulted on average in 1.37 kg more weight loss than with metformin alone. In the subsequently conducted Study 102034, the dapagliflozin dose of 10 mg proposed for marketing was used in a similar protocol and the findings were essentially the same as those of Study 102021. With the higher dapagliflozin dose given alone, HbA1c change at 24 weeks was similar to that for 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

proportions of subjects in the various treatment groups achieved HbA1c ≤7% as in Study 102021. Mean weight loss on combination therapy was 3.35 kg compared with 2.75 kg on dapagliflozin alone and 1.32 kg on metformin alone.

These studies indicate that dapagliflozin in initial combination therapy with metformin achieves a significantly greater reduction in HbA1c than is achieved with metformin alone, the quantum of difference in HbA1c of 0.54-0.70% being clinically significant. Approximately 2 kg greater weight loss was also achieved with the combination therapy. There is no long term extension data on this therapeutic combination.

Add-on combination with metformin

Supporting this indication are 2 trials, both with 78 week long term extensions. Study MB 102014 randomised 546 poorly controlled T2DM subjects to a variety of doses of dapagliflozin (noted above) or placebo. A 10 mg dapagliflozin dose produced a 0.84% reduction in HbA1c as compared with 0.30% for 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 of treatment, as was evident for the dapagliflozin groups in many of the studies in the current submission irrespective of the background therapeutic combination. Weight loss was 0.89 kg with placebo and 2.86 kg for the dapagliflozin 10 mg group. Outcomes for HbA1c and weight loss were equally satisfactory in those subjects who were worst controlled and most obese at baseline. A pivotal aspect of this trial is the long term extension in which there was 98% participation. Some 95/119 of the 10 mg dapagliflozin subjects completed a total of 102 weeks treatment with a maintained 0.80% reduction in HbA1c and maintained reduction in FPG. At 102 weeks the mean body weight change was -3.1 kg relative to placebo.

Study D1690C000012 was a body weight/body composition study with no glycaemic endpoints and is a supportive study only. Subjects taking metformin were randomised to dapagliflozin 10 mg or placebo. At 24 weeks, weight loss was 2.96 kg in the dapagliflozin 10 mg group compared with 0.88 kg for placebo (p<0.0001). Waist circumference and % total body fat mass also declined and magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) techniques showed reduction in both abdominal subcutaneous and visceral adipose tissue. Results from the 78 week long term extension were not reported as this was still in progress at the time of data submission.

Additional support for the indication of add-on combination with metformin comes from Study D1690C00004 which compared dapagliflozin with a sulphonylurea (glipizide) as add-on treatment for T2DM subjects poorly controlled on metformin. At 52 weeks, HbA1c had fallen by 0.52% in both groups and non inferiority of the two treatment approaches was clearly shown. Body weight fell by a mean 3.22 kg in the dapagliflozin group compared with a rise of 1.44 kg in body weight in the glipizide group. The dapagliflozin subjects experienced less hypoglycaemia. The importance of this study is that it demonstrates dapagliflozin as an alternative to sulphonylurea therapy in the setting of patients who are failing on initial therapy with metformin.

Together, these studies provide strong evidence of efficacy of dapagliflozin as add-on therapy for subjects failing with metformin alone, including maintenance of glycaemic response and weight reduction over 1-2 years.

Add-on combination with a sulphonylurea

A single study, D1690C00005, evaluated the use of dapagliflozin 2.5, 5 and 10 mg by comparison with placebo in subjects taking glimepiride 4 mg daily. This trial recruited a population of metformin non users, many of whom were significantly renally impaired, which makes it a "real world" study in the sense that T2DM patients in whom metformin is

contraindicated or not tolerated are those in whom this combination might be considered, particularly in the Australian context.

Some 87% of subjects completed the entire 48 week study, including the extension period. At Week 24 HbA1c had fallen 0.68% with dapagliflozin 10 mg compared with 0.15% for placebo (p<0.0001). FPG fell by 1.5 mmol/L and weight by 2.26 kg for dapagliflozin 10 mg subjects (compared to 0.72 kg in the placebo group). Some 32.7% of dapagliflozin 10 mg subjects achieved HbA1c <7% (compared to 12.6% of placebo). The HbA1c response was maintained at 48 weeks (dapagliflozin 10 mg, -0.73%: placebo, -0.41%). There was a significant interaction between HbA1c response at 24 weeks and category of renal function, although those with moderate impairment still had a reasonable response (change from baseline -0.63%). These data are discussed further below.

Add-on combination therapy with a thiazolidinedione

Study MB 102030 examined the efficacy of dapagliflozin 5 mg and 10 mg and placebo, added to pioglitazone 30 mg or 45 mg if tolerated, being given to T2DM patients as monotherapy but with poor glycaemic control. Given this somewhat unlikely clinical scenario as a starting point, recruitment to this study was a very complex process and the majority of subjects (limited to 67% of randomised set by study protocol) had been on a variety of antidiabetic regimens and were switched to pioglitazone for the purpose of the study. It is therefore probable that this study population had an unusually high degree of heterogeneity with respect to previous diabetic medication history and might be variously liable to either respond to or relapse on any new regimen. Despite these limitations, a difference from placebo in HbA1c response at 24 weeks was shown; -0.40% and -0.55% for the 5 mg and 10 mg dapagliflozin doses (p<0.0001) respectively. Consistent with the complexities of recruitment, the placebo response itself was clinically significant at -0.42%. These placebo subjects gained an average 1.64 kg, possibly reflecting the recent introduction of pioglitazone. With combination pioglitazone/10 mg dapagliflozin, a mean weight loss of 0.14 kg was found. FPG and 2 h post challenge plasma glucose outcomes were also improved in the dapagliflozin group as in other studies.

This study also provides *further evidence of greater efficacy with 10 mg compared with 5 mg dapagliflozin*.

At 48 weeks, excluding data of 11.4% of subjects who had required rescue therapy, the placebo subtracted mean change in HbA1c for the 10 mg dapagliflozin group was -0.67%. This is an underestimation of its efficacy in the sense that a much higher proportion (33.8%) of placebo subjects had required rescue.

The results indicate that addition of dapagliflozin 10 mg to maximal pioglitazone therapy resulted in a gain in glycaemic control of 0.55-0.67%, comparable to that achieved with additions to other oral agents or when given as monotherapy. The combination treatment was also preventive of the weight gain which occurs (and was noted in this study) with pioglitazone given alone. Although based on a single study, the conclusions appear robust, based on comparison of treatment groups with n=140 and with high statistical significance.

Add-on combination therapy with insulin

This indication is also supported by a single study, D1690C00006. This is another "real world" study with a typically obese, insulin resistant and poorly controlled T2DM population with average 13.6 years since diagnosis and six years on insulin therapy. Subjects were taking a variety of other oral agents as is common. Median insulin dose was 65 units. Dapagliflozin was added in three doses; 2.5, 5 and 10 mg daily or placebo. There were 194 subjects in the 10 mg group and HbA1c was reduced by 0.90% at 24 weeks compared with 0.30% for placebo (p<0.0001). Significant changes were also noted for body weight (which was down a mean 1.69 kg) and FPG (down 1.0 mmol/L) as compared

with placebo. These parameters were virtually unchanged in the placebo group. There was little overall change in insulin dose; the changes were highly variable between subjects although less dapagliflozin subjects required upward titration.

At the end of a 48 week extension (total 72 weeks) completed by >80% of subjects, a benefit of 0.50% in HbA1c reduction was still evident for the 10 mg dapagliflozin subjects. Body weight had not changed further but a significant finding was that insulin dosage was remaining stable whereas it had increased by an average of 10.5 units (16%) in the placebo group.

The study documents indicate that a further 56 week extension period is ongoing.

Supportive data for this indication is also found in the Phase IIb pilot Study MB 102009 of efficacy and safety of dapagliflozin in T2DM subjects who had uncontrolled disease on combination therapy with metformin and/or thiazolidinedione and insulin; the mean HbA1c rose by 0.09% in the placebo group and fell by 0.61% in the 10 mg dapagliflozin group.

In summary, dapagliflozin in combination with insulin produced an average additional 0.5% improvement in HbA1c, which was maintained for more than one year and was effective in preventing upward creep of insulin dosage.

Clinical studies in special populations

Impaired renal function

The pharmacodynamic (glucuretic) response to dapagliflozin is impaired in the presence of impaired renal function as discussed above. Some reduction of efficacy can therefore be anticipated in this situation. Study MB 102029 recruited subjects who had T2DM and moderate renal impairment defined as an eGFR 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2 and inadequate glycemic control, defined as HbA1c ≥ 7.0% and ≤ 11.0%; mean HbA1c at baseline was 8.5%. The findings of this study are summarised as; at 24 weeks, HbA1c fell by approximately 0.30% in all groups whether receiving dapagliflozin 10 mg, 5 mg or placebo. The dapagliflozin subjects lost approximately 2 kg by comparison with placebo (significance not tested, as no different shown for primary efficacy parameter). At 52 weeks, there was a placebo adjusted difference in HbA1c of 0.30% between the 10 mg dapagliflozin and placebo subjects; furthermore, 11.7% of the dapagliflozin subjects had achieved HbA1c <7% compared with 3.7% of placebo subjects.

Further evidence on this point is found in the sub analysis by category of renal impairment carried out on the data from Study D1690C00005. There was a significant (p= 0.0115) treatment interaction with renal function category as defined by GFR. For those subjects with normal renal function in the 10 mg dapagliflozin group (47/151), the mean change in HbA1c from baseline to 24 weeks was 0.89%, compared with 0.80% and 0.63% in the mild and moderately impaired (eGFR 60 – 90 and 30 - 59 mL/min/1.73 m^2 respectively) groups.

In the draft PI a case is made for use of dapagliflozin in those moderately renally impaired subjects with eGFR ≥45 to <60 mL/min/1.73 m^2 on the basis of a subgroup analysis from Study MB 102029 for this particular category (denoted 3A) of renal dysfunction. This subgroup analysis was not referred to in the study report or in the study narrative in the sponsor's *Summary of Clinical Efficacy*. It is referred to in the discussion section of that document and is reproduced below (Table6).

Table 6. Subgroup analysis from Study MB 102029 (subject eGFR range 45 -<60 mL/min/1.73m²).

	PLACEBO N=41	DAPA 5MG N=35	DAPA 10MG N=33
SUMMARY STATISTICS			
N#	40	35	32
BASELINE MEAN (SD)	8.78 (1.318)	8.13 (0.928)	8.25 (0.892)
WEEK 24 MEAN (SD)	8.62 (1.201)	7.93 (1.086)	8.03 (1.002)
MEAN CHANGE FROM BSL (SD)	-0.16 (1.374)	-0.20 (0.941)	-0.22 (0.797)
ADJUSTED CHANGE FROM BASELINE			
MEAN (SE)	-0.11 (0.2339)	-0.47 (0.2483)	-0.44 (0.2546)
95% 2-SIDED CI	[-0.57, 0.35]	[-0.97, 0.02]	[-0.94, 0.07]
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS PLACEBO			
MEAN (SE)		-0.37 (0.2322)	-0.33 (0.2376)
95% 2-SIDED CI		[-0.83, 0.10]	[-0.80, 0.14]

Note that the demonstration of a difference in HbA1c change from baseline between placebo and dapagliflozin in this relatively small group of subjects relies heavily on the adjustment factor in the statistical model. Even with this correction, the improvement in HbA1c of 0.33% would be of little therapeutic benefit. Furthermore, the difference between placebo and dapagliflozin groups has not been statistically tested and given that the 95% CI cross zero might not achieve this. In summary the data and Study MB 102029 in particular, *show that dapagliflozin is relatively ineffective in reducing blood glucose in the presence of moderate renal impairment. The evidence for benefit of using it in the subgroup of patients with eGFR values in the 45-60 mL/min/1.73 m² range is marginal.*

Use in children

No studies were included in the application. However, a paediatric development plan for children aged 10-18 years has been designed and has been approved by the European Medicines Agency with a waiver for children aged below 10 years on the grounds that the relevant condition (T2DM) does not occur in that group. The studies detailed in the plan were at the time of the documentation (11/6/2010) still in progress.

Analysis performed across trials (pooled analyses and meta-analysis)

The sponsor has conducted a pooled analysis of the Phase III studies which is referred to in the sponsor's *Clinical Overview*, the sponsor's *Summary of Clinical Efficacy* and elsewhere. Change from baseline in HbA1c (primary efficacy parameter) was examined in pre specified subgroup categories which included age, gender, race, female age, ethnicity, geographical region, baseline HbA1c, baseline BMI, baseline eGFR, and duration of diabetes. The subgroup analyses show greater reductions in HbA1c (defined by interaction p value <0.1) for subjects with more poorly controlled diabetes (higher baseline HbA1c), better renal function (higher eGFR) and younger age. These findings are not surprising: as pointed out above, the pharmacodynamic action of dapagliflozin is dependent on the blood glucose level and the glomerular filtration rate and it would therefore be expected to be more effective in this situations described. The finding regarding age was of uncertain significance in view of the potential confounding factor of decline in renal function with age which was not accounted for in the statistical model. The sponsor's *Clinical Overview* refers to a further analysis done after controlling for category of renal function, which appears to have excluded age as an independent factor (interaction p value= 0.2903). This leaves the level of diabetes control and renal function as the only significant variables affecting efficacy, consistent with pharmacodynamic expectation.

Evaluator's overall conclusions on clinical efficacy

For all of the claimed indications, whether given as monotherapy, in initial combination with metformin or as add-on therapy to metformin, sulphonylurea, thiazolidinedione or

insulin, dapagliflozin shows efficacy in the control of T2DM with modest reductions in HbA1c in the range 0.5%-0.8% being achieved rapidly and maintained after 24 weeks treatment. From the submitted evidence, the quantum of benefit is slightly stronger for dapagliflozin given as add-on therapy to metformin, in combination with metformin as initial therapy or as monotherapy in drug naïve subjects. A significant proportion of the studies supporting the other indications show HbA1c improvements only just over 0.5% which is arbitrarily regarded as the minimum worthwhile improvement with therapy. To some extent, this may reflect the populations of those studies including a higher proportion of subjects whose diabetes was of longer duration or had already proved resistant to other therapies. Longer term maintenance of improved glycaemic control was not shown or not tested for in the studies supporting monotherapy or initial combination therapy but was shown for varying intervals between 48 and 102 weeks for all of the add-on indications.

Use as add-on therapy in combination with a sulphonylurea and with a thiazolidinedione is in each case supported by only a single study using glimepiride in the former instance and pioglitazone in the latter. Both these studies show differences between the actively treated and placebo groups with high levels of significance and are regarded as sufficient evidence. Because the mechanism of action of dapagliflozin is quite distinct from that of sulphonylureas or thiazolidinediones, it is felt that the demonstrated add-on benefit can in each case be regarded as a class effect. Dapagliflozin does not significantly affect the PK of either glimepiride or pioglitazone (see above) and given its overall low propensity for drug-drug interaction, it seems unlikely that it would have any effects on other drugs of these classes which might interfere with the benefits of co administration.

The quantum of glycaemic improvement demonstrated with use of dapagliflozin is similar to that supporting the use for similar indications of sitagliptin (0.65-0.7%[36]) but somewhat less than that which supports the use of thiazolidinediones. For pioglitazone, HbA1c reductions of 1.3-1.4% were found for treatment naïve subjects or when used as add-on therapy to sulphonylurea and 0.8% for add-on treatment to metformin; and for rosiglitazone, in the range 0.8-1.4% when used as an add-on treatment to metformin[36].

There is good evidence throughout the efficacy studies of improvement in post prandial as well as fasting glycaemia. An additional benefit is loss of body weight, averaging 2-3 kg over six months in most studies. The amount of weight loss is small in the context of the obesity often associated with T2DM and would not support the use of dapagliflozin for the primary purpose of weight reduction but is in contrast to the weight gain which is a frequent unwanted effect of virtually all diabetes therapies apart from metformin. Body composition Study D1690C000012 showed the weight to be lost from both subcutaneous and visceral adipose tissue and therefore likely to be a positive health benefit.

The efficacy of dapagliflozin is reduced with progressive impairment of renal function. In subjects with mildly impaired function (eGFR eGFR 60 to 90 mL/min/1.73 m^2) efficacy is maintained but is significantly impaired below the level of therapeutic benefit in those with moderately impaired function (eGFR 30 to 59). The sponsor claims efficacy in a subgroup of moderately impaired subjects with eGFR 45 to 59 mL/min/1.73 m^2 but the evidence for this is not persuasive.

Safety

Introduction

Presentation of safety data in this report is in three parts. Firstly, there is the broad spectrum of adverse events (AE) and serious adverse events (SAE), including deaths, reported to and collated by trial investigators in each study report. Secondly, there are areas of special interest related to the mechanism of action of dapagliflozin which were

identified by the sponsors as safety risks early in the development program and which were specifically investigated and documented in each study report. These include hypoglycaemia, genital infection, urinary tract infection, renal function, hypovolaemia-related events, possible hepatic injury, and haemoconcentration (increased haematocrit) and are discussed below. Thirdly, more recently areas of potential concern have arisen, either as a result of regulatory requirement or clinical observations from the trial data, which have required or may require further assessment by the sponsor. These include the potential for increased cardiovascular events, a possible risk of osteoporosis and the observation of clusters of cases of breast and bladder cancer and these are discussed in separate sections below.

The incidence of AE, SAE, deaths and events of special interest in the studies in the application has been evaluated. Summary data on exposure and adverse events presented in the sections *Patient exposure, Adverse events, Serious Adverse Events* and *Laboratory Findings* are is drawn from the sponsor's *Summary of Clinical Safety* and other relevant parts of the application.

Patient exposure

Exposure to dapagliflozin is limited to the clinical trial program as there is no post marketing experience at this stage but documentation of this is complex, particularly in relation to the proposed 10 mg dosage as many of the trials contains multiple dosage regimens. In the 40 included studies, 4922 subjects received at least one dose of dapagliflozin and of these 1373 received 10 mg doses. 1193 subjects received 10 mg doses for the 24 week short term phase of the placebo controlled studies and of these, 768 continued with 10 mg daily doses in longer term extensions of 24 weeks or longer.

Overall breakdown of exposure to various doses is as follows:

Exposure in the 26 clinical pharmacology studies has been noted above. These were conducted in 688 subjects of whom 635 were exposed to dapagliflozin. This total includes subjects exposed in 2 studies which were terminated early. Of the total number of subjects:

- 554 were healthy subjects (518 exposed to dapagliflozin)
- 32 were subjects with T2DM and renal impairment (all exposed to dapagliflozin)
- 18 were subjects with hepatic impairment (all exposed to dapagliflozin)
- 84 were subjects with T2DM (67 exposed to dapagliflozin).

During the Phase IIb/III studies, the number of subjects with T2DM exposed to doses of dapagliflozin determined to be therapeutically active (2.5, 5, 10, 20, and 50 mg) was as follows:

- Exposure to dapagliflozin 2.5 mg or higher for at least:
  - one dose: 4287 subjects
  - 6 months exposure: 3333 subjects
  - 12 months exposure: 2232 subjects
  - 18 months exposure: 1317 subjects
  - 24 months exposure: 441 subjects
- At least one dose exposure to control: 1941 subjects

Adverse events

In this section, comment will be restricted to AE reporting by subjects receiving 5 mg or 10 mg doses of dapagliflozin, or placebo. Overall during placebo controlled double blind therapy, AE were reported by slightly higher proportions of 5 mg (61.9%) and 10 mg (61.5%) dapagliflozin subjects compared to placebo subjects (56.9%). Some of this increase was related to reporting of hypoglycaemia by 11.4% and 10.7% of the dapagliflozin group subjects respectively, compared with 8.0% by placebo subjects. There was overall also an increased incidence of reporting of symptoms suggestive of genital infection (GI) or urinary tract infection (UTI). This appears as a consistent finding in the reports of the individual clinical studies. Apart from these categories of AE, the majority of events reported by subjects were non-specific, mostly respiratory or gastrointestinal symptoms and showed no maldistribution between the placebo and dapagliflozin groups or any unusual qualitative pattern.

More specific information appears in the listing of those AE which were classified by individual (blinded) trial investigators as being adverse drug reactions, that is, possibly treatment related during the short term (mostly 24 week) double blind periods, stratified by system organ class (SOC) and which occurred more commonly in dapagliflozin than placebo-treated subjects are shown in Table 7 below.

Table 7. Adverse drug reactions, possibly treatment related, reported in the short term and which occurred more commonly in dapagliflozin than placebo-treated subjects.

SOC- Preferred Term	Dapagliflozin 5 mg N= 1145	Dapagliflozin 10 mg N= 1193	Placebo N= 1393
Metabolism and Nutrition Disorders			
Hypoglycemia[a]	Very Common (10.9%)	Very Common (10.2%)	Common (7.0%)
Infections and infestations			
Genital infection[b]	Common (5.7%)	Common (4.8%)	Uncommon (0.9%)
Urinary tract infection[c]	Common (5.7%)	Common (4.3%)	Common (3.7%)
Musculoskeletal and Connective Tissue Disorders			
Back pain	Common (3.1%)	Common (4.2%)	Common (3.2%)
Renal and Urinary Disorders			
Polyuria[d]	Common (2.9%)	Common (3.8%)	Common (1.7%)
Dysuria	Common (1.6%)	Common (2.1%)	Uncommon (0.7%)
Metabolism and nutrition disorders			
Dyslipidemia	Common (2.1%)	Common (2.5%)	Common (1.5%)

Hypoglycaemia, GI, UTI, urinary symptoms and dyslipidaemia were all amongst the classes of events classified as areas of special interest in the development program and are discussed below; the difference with back pain does not appear significant and in general there were no other types of AE which appear to be of disproportionate incidence in the dapagliflozin treated subjects or which appear likely to be related to dapagliflozin.

Data from the long term extensions exhibited a similar pattern of AE except for the emergence of some disparities in serious adverse events (SAE) as described in the following section.

Serious adverse events and deaths

SAE were reported by 340/4287 (7.9%) of dapagliflozin (all dosages) subjects by comparison with 156/1941 (8.0%) of the subjects in the control group.[40] Some specific categories of SAE were reported in a larger proportion of dapagliflozin than placebo subjects and these included pneumonia (0.3%, 0.2%), breast cancer (0.2%, 0.0%) and cholelithiasis (0.2%, 0.0%). Angina pectoris was also in this category (0.3%, 0.1%) although it is noted that a reverse trend was apparent for acute myocardial infarction (0.2%, 0.3%). The finding on cholelithiasis appears to be a chance event as other classifications of AE pertaining to gallstones or biliary tract disease were evenly distributed. The 8 cases of breast cancer, together with an additional case subsequently discovered are the subject of a special report discussed below. Cases of bladder cancer, a condition which had not originally been identified as being of special risk, have also been reported since the sponsor's *Summary of Clinical Safety* was compiled and are discussed below.

Fractures did not occur any more commonly in dapagliflozin as opposed to placebo subjects, with the specific exception that in Study MB 102029 they occurred in 3/83 dapagliflozin 5 mg and 7/85 dapagliflozin 10 mg subjects and no event in placebo group during the 52 weeks of the study. These and related findings regarding possible osteoporosis are discussed further below.

Urinary tract stones had been identified as a possible AE of special interest in view of the mechanism of action of dapagliflozin but did not become evident in the clinical monitoring program.

Other classifications of SAE, mostly non-specific infections or other conditions commonly occurring in association with T2DM, were distributed evenly between the placebo and dapagliflozin treated groups.

Deaths

No deaths occurred during the PK/PD studies. Over the entire Phase IIb/III program, including the long term extension periods, deaths were evenly balanced between control and dapagliflozin treated subjects, as shown below in Table 8.

Table 8. Deaths reported in the Phase IIb/III program

All Control (N= 1941)	Dapagliflozin Total (N = 4287)
10 (0.5%)	21 (0.5%)

Most deaths were due to major cardiac or vascular events attributable to the recognised co morbidities of T2DM. No association with the study medication is suggested.

Laboratory findings

A dose related change in haematocrit observed in dapagliflozin treated subjects was identified as an area of special interest and is discussed further below. Likewise, increases in serum parathyroid hormone (PTH) which were observed in a number of studies are discussed in relation to osteoporosis risk below, as are abnormalities and liver function. A sustained decrease in serum uric acid resulting from the uricosuric action of dapagliflozin was noted as described above (under *Secondary Pharmacodynamics*). Apart from these defined areas, no specific pattern of AE relating to laboratory parameters was evident.

[40] Sponsor comment: "The numbers include patients from all Phase IIb/III studies including active contol Study 004."

Safety in special populations

Renally impaired population: safety aspects in renally impaired subjects (Study MB 102029) are fully discussed as an area of special interest below.

Elderly subjects: distribution of AE in an elderly population, loosely defined as subjects aged ≥65 years, of which there were 1166 in the study population.[41] No trends differing from the general study population were observed. The sponsor's *Clinical Overview* also makes reference to the 169 subjects included in the studies who were aged ≥75 years. No numerical or statistical observations are made but a precautionary statement is included that the effect of ageing on factors such as renal function and vascular sufficiency should be taken into account in the use of dapagliflozin with regard to possible adverse effects such as dehydration, hypertension and associated decline in renal function.

Pregnancy, breastfeeding: there have been no studies on this topic. Essentially use is discouraged or contraindicated in these groups, although the PI is ambivalent about pregnancy.

Areas of special interest

Identified or anticipated adverse effects

Hypoglycaemia

Although it is rightfully included as an area of special interest, the study outcomes do not identify hypoglycaemia as an area of special safety concern for this evaluation. The incidence varied according to which other diabetes medication was being co administered. In the studies of monotherapy or combination with metformin, the proportion of subjects with events of hypoglycaemia (including minor events characterised only by a capillary blood glucose measurement) was low, between 2.0 and 3.1%, and evenly distributed between placebo and active treatment groups. The incidence of hypoglycaemia was higher when dapagliflozin was being given together with an agent in itself prone to cause hypoglycaemia, particularly sulphonylurea (D1690C00005) or insulin (D1690C00006). This is consistent with the action of dapagliflozin being proposed to increase the effectiveness of these therapies and in clinical practice would be countered by down titration of dosage of the (for example) sulphonylurea. This was, in general, not allowed for in the study protocols.

As a positive outcome, it should be noted that in the active comparator Study D1690C00004, comparable glycaemic control was achieved on dapagliflozin by comparison with glipizide with a considerable *reduction (*3.5% versus 40.8%) in the incidence of hypoglycaemia.

In the spectrum of oral hypoglycaemic therapies, dapagliflozin is at the low end for hypoglycaemic risk.

Genital infections

Genital infections, particularly vulvovaginal candidiasis in females and less commonly balanitis in males, are well recognised complications of uncontrolled diabetes. The conventional explanation being that the glucose which appears in the urine when blood glucose exceeds the renal threshold acts as a nutrient substrate for the growth of microorganisms. It has sometimes been argued that this phenomenon has less to do with glycosuria than with systemic effects of hyperglycaemia on immune function and perhaps the results of the studies in this application provide a definitive answer to that question. In

[41] Sponsor comment: "This is the number of subjects with age >=65 but < 75. There were 1335 subjects with age >=65 in the Phase IIb/IIIpool."

all of the Phase IIb/III studies and even some of the PK/PD studies, there has been an obvious and consistent increase in the incidence of genital infections in the dapagliflozin treated groups.

In the pool of placebo controlled studies, the overall incidence of events suggestive of genital infection was 7.0% for both 5 mg and 10 mg dapagliflozin compared with 2.1% for placebo subjects. Most of this risk applied to females. The majority (>97%) of these events were mild/moderate and resolved with or without physician intervention; T2DM patients have an awareness of the need for antifungal agents, which in most regions are available over the counter. The sponsor's contention that while it is important for this risk to be identified, it is manageable, was considered as appropriate

Urinary tract infections

Urinary tract infections, sometimes asymptomatic, are also recognised as a complication of uncontrolled diabetes for the same reasons as outlined in the previous section. They were also more common in the dapagliflozin treated subjects, occurring in 7.3% and 6.5% of 5 and 10 mg treated subjects respectively, compared with 4.2% of placebo subjects. Apart from being less prevalent overall than genital infections, the gender difference was also less marked. The great majority of UTIs involved the lower urinary tract only, with few episodes of pyelonephritis, most infections resolving readily either spontaneously or with treatment. The same comment applies as for genital infection that urinary tract infection is an important area of risk requiring physician and patient education with respect to dapagliflozin but is not a serious safety concern provided it is appropriately managed.

Renal function

Renal function was closely monitored in trial subjects in view of the high background incidence of renal disease in T2DM and because of the renal action of dapagliflozin, particularly its diuretic like action which would have the potential through mechanisms such as volume depletion and blood pressure reduction to precipitate impairment of renal function. Consistent with this, small decreases in eGFR (essentially, increases in plasma creatinine) were seen as early as one week following administration of dapagliflozin. This trend reversed with time and over the short-term period of the double blind studies, a small *increase* in mean eGFR values was seen in all treatment groups from baseline to Week 24: 1.4 and 1.2 mL/min/1.73 m^2 in the dapagliflozin 10 mg and placebo groups, respectively. There was an increased incidence of AE terms related to renal impairment or failure (mainly increased serum creatinine) in the dapagliflozin groups: 1.3% with 5 mg and 0.9% to 10 mg dapagliflozin, compared with 0.9% with placebo. This risk is clearly dependent on the baseline level of renal function; the proportions of subjects (dapagliflozin total versus placebo) with events of renal impairment or failure by eGFR subgroup were as follows (from table 67, appendix 230B of Summary of Clinical Safety):

- ≥ 30 to < 60 mL/min/1.73 m2: 23(8.3%) versus 6 (5.6%)
- ≥ 60 to < 90 mL/min/1.73 m2: 13 (0.7%) versus 4 (0.5%)
- ≥ 90 mL/min/1.73 m2: 2 (0.2%) versus 2 (0.4%)

Simple elevation of serum creatinine to ≥ 1.5 times the upper limit of normal (ULN) occurred in similar numbers of active and placebo treated patients. More serious renal adverse events were rare. Two deaths occurred in the setting of decompensated renal failure; one with progressive heart failure and the other following acute myocardial infarction. The occurrence of such events in a large population of T2DM patients of this age group is seen as consistent with expectation.

The safety of using dapagliflozin in subjects with *established* renal dysfunction was examined in Study MB 102029, the efficacy aspects of which have been discussed in detail in the section *Clinical studies in special populations* above. As part of this assessment, the

changes in eGFR in the placebo and dapagliflozin treated groups from baseline to Week 52 were measured and are shown below in Table 9.

Table 9. Changes in eGFR in the placebo and dapagliflozin treated groups from baseline to Week 52 from MB102029.

	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
SUMMARY STATISTICS			
N#	49	64	63
BASELINE MEAN (SD)	47.39 (10.592)	44.21 (9.020)	43.46 (8.956)
WEEK 52 MEAN (SD)	44.81 (12.951)	42.13 (9.700)	39.00 (8.347)
MEAN CHANGE FROM BASELINE (SD)	-2.58 (8.104)	-2.08 (7.951)	-4.46 (7.730)
ADJUSTED CHANGE FROM BASELINE			
MEAN (SE)	-1.35 (1.5705)	-2.00 (1.4426)	-4.47 (1.4501)
95% CONFIDENCE INTERVAL	(-4.45, 1.75)	(-4.85, 0.85)	(-7.33, -1.61)
DIFFERENCE IN ADJUSTED CHANGE FROM BASELINE VS. PLACEBO			
MEAN (SE)		-0.65 (1.4546)	-3.12 (1.4609)
95% CONFIDENCE INTERVAL		(-3.52, 2.22)	(-6.00, -0.24)

While the difference versus placebo for this moderately renally impaired group (eGFR ≥30 and <60) has not been tested statistically, eGFR in the dapagliflozin 10 mg group fell by approximately 10% and the 95% CI for the difference from placebo do not cross zero. The evidence for a significant deterioration in renal function is therefore somewhat more persuasive than the claimed evidence of benefit for a subgroup of these subjects discussed in relation to this study above (*Clinical studies in special populations*). The study report notes in its concluding comments that reductions in eGFR were seen as early as Week 1 in the dapagliflozin groups but then "tended to stabilise" whereas in the placebo group a more gradual fall of eGFR occurred. This observation is followed by a final statement that *"The data suggest that dapagliflozin, when added to existing therapeutic regimens, may promote weight loss or prevent weight gain, reduce blood pressure, **stabilize eGFR**, reduce the risk of hyperkalemia,…"*, suggesting that this effect of dapagliflozin on eGFR is *beneficial* which is hardly a reasonable conclusion.

The sponsor also presents discussion on the safety profile of this 3A subgroup of moderate renal impairment (eGFR ≥45 and <60) in the sponsor's *Summary of Clinical Safety*. This attempts to make the case that safety is preserved in this subgroup by comparison with the moderately renally impaired group overall but is unpersuasive. It refers to these subjects as having an increased incidence of AE of renal impairment or failure, increases in MAs of creatinine, increased PTH and phosphate levels and increased AE of hypotension. It does not give a comparison of the overall change in eGFR comparable with the entire moderately impaired group as shown in the table above.

In summary, the data suggests that dapagliflozin may cause minor but significant deterioration in renal function particularly in subjects whose renal function is already moderately impaired. These changes are probably reversible although this has not been clearly established.

Hypovolaemic events

Not surprisingly, the pattern of incidence of AE in this category closely mirrors that of impaired renal function events described in the previous section. The mechanism of action of dapagliflozin in promoting urinary loss of both sodium (co-excreted with glucose) and water (due to osmotic effect of glucuresis) can be predicted to have a volume depleting effect with reduced blood pressure as an outcome, and consequent reduction in GFR as outlined above.

Reported AE of hypotension, dehydration or hypovolaemia were in the pool of placebo controlled studies more common with dapagliflozin (0.7%) than with placebo or other comparator (0.4%). Two SAE were reported, both of syncope. Overall, the fall in systolic or

mean blood pressure in the dapagliflozin treated subjects was small (3-5 mmHg in most studies) and there was no increase in the incidence of orthostatic hypotension.

Once again as with the renal impairment AE, there were identifiable risk factors which favoured a high incidence of hypovolaemia associated events in the dapagliflozin groups including age ≥65 years, baseline EGFR <60 and coadministration of loop diuretics. It will be necessary to advise caution in these clinical circumstances which are identified by the sponsor as reasons for considering the 5 mg dosage; amongst a small subgroup of subjects who received loop diuretics there were fewer adverse events of hypotension, dehydration or hypovolaemia in those using the 5 mg dapagliflozin dose (sponsor's *Clinical Overview*).

Hepatic function

In line with a routine FDA requirement, liver function tests were monitored throughout the clinical development program with specific attention to levels of serum transaminase enzymes (AST or ALT) exceeding 3 times the ULN. Such abnormalities were found in 4.5% of placebo subjects and 3.9-4.7% of dapagliflozin subjects, without any evidence of dose relationship. A single patient in Study D1690C00004 being treated with metformin and 5 mg dapagliflozin developed an acute hepatitis which improved on withdrawal of study drug but required immunosuppressive agents to maintain the response so that the differential diagnosis between autoimmune and drug induced hepatitis is in doubt. Nevertheless, the sponsor indicates that drug induced hepatitis has been identified as a potential risk and will be monitored.

Increased haematocrit

A consistent abnormality observed in all of the clinical trials was an increase in haematocrit which was evident by Week 12 and persisted thereafter. At Week 12-16, the average absolute increase in haematocrit in the pooled studies for dapagliflozin 10 mg was 2.15% (for example, a change in haematocrit from 40% to 42.15%), with no discernible change in placebo subjects. At Week 76 in the long term studies, the average mean increase in 10 mg dapagliflozin subjects had risen slightly more to 2.54%. There is very little between-individual variation in this response which means firstly that it occurs in the great majority of subjects and secondly that substantially larger upward variations in haematocrit occurred infrequently; although marked abnormalities (MAs) of haematocrit or haemoglobin were observed more in dapagliflozin and placebo subjects, they occurred in a very small proportion of subjects. Haematocrit >55% or haemoglobin >18 g/dL were reported in <2% of dapagliflozin subjects and <0.1% had haematocrit values >60%. These values occurred without any adverse clinical thromboembolic event except for one subject who had a baseline haematocrit of 54% which rose to 55% during the study and multiple other risk factors.

The small between-individual variation in this phenomenon is quantified in the PPK report. Exposure-response analyses conducted with data from 1524 subjects collected up to Week 24 in Studies MB102013, MB102032 and D1690C00006 predicted that the 10 mg once daily dose would result in a 2.44% increase in haematocrit, with 5th, 95th percentile limits of 0.432, 3.38. This suggests that 5% or less of subjects would develop a change in haematocrit which would exceed, for example, the physiological difference between male and female. Nevertheless, increased haematocrit has been identified by the sponsor as a potential risk which will be monitored.

The cause of this abnormality is not clear. The obvious suggestion is that it might be due to mild chronic dehydration, although if this were the case an upward shift in serum osmolality flagged by an increase in serum sodium would be expected particularly as there has been a fall in blood glucose during the course of the study. Inspection of the serum sodium data which was collected regularly through the studies reveals this not to be so for the general body of subjects in whom the haematocrit increase is observed, although

occasional incidences of more severe hypernatraemia (>150 mmol/L) were observed in more dapagliflozin (1.4%) than placebo (0.7%) subjects.

Possible or potential adverse effects

Cardiovascular events

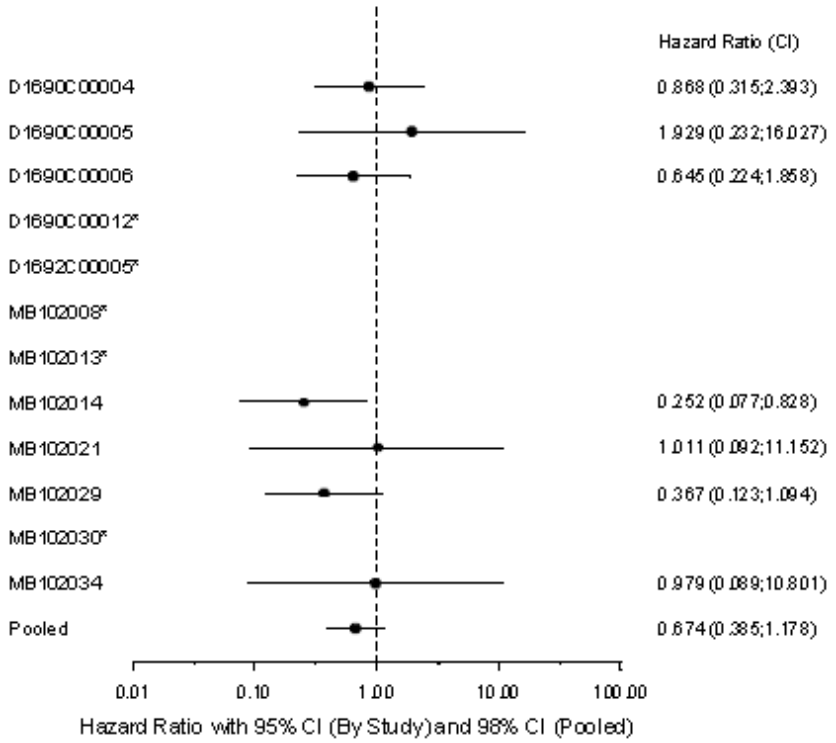
In line with a FDA regulatory requirement that risk of cardiovascular events be assessed as part of the investigation of any new diabetes therapy, the sponsors have conducted a meta-analysis of such events occurring during the Phase IIb/III trials. The specific FDA requirement is that: "*For completed studies, before submission of the new drug application (NDA), sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval (CI) for the estimated risk ratio is less than 1.8*".[42] Suspected events occurring during the trials were independently adjudicated against predetermined criteria for various categories of cardiovascular events and a primary composite endpoint defined, which is the time to first event of cardiovascular death, myocardial infarction, stroke or hospitalisation for unstable angina. A secondary composite endpoint added events of unplanned coronary revascularisation or hospitalisation for heart failure to the above criteria. Data were collected for all subjects given doses of dapagliflozin 2.5 mg or above (considered as the therapeutic range) and corresponding comparator subjects and the comparison undertaken between the groups using a Cox proportional hazards model. The full details of the statistical methodology are summarised in a report of the meta-analysis.

The estimated hazard ratio for the primary composite endpoint was 0.674 (98% CI: 0.385, 1.178; 95% CI: 0.421, 1.078). The point estimate, which is below 1, together with the upper bound of the 98% CI being below both 1.8 and 1.3, indicate that treatment with dapagliflozin is not associated with an unacceptable increase in cardiovascular risk. As a consequence, the sponsor indicates that the FDA criteria are fulfilled. It is also stated that the design of the meta-analysis complied with European (EMEA) requirements. A Forest plot of the hazard ratio and 95% CI from this analysis for the short term and long term period showing the pooled analysis and stratified by included studies is shown below (Figure 4).

Supportive analyses by dose were consistent with these outcomes. The hazard ratios for the 5 mg and mg 10 mg doses respectively were 0.529 and 0.564, with the upper bound of 98% CI remaining below 1.3. The comparator group does contain one active (glipizide) control study, D1690C00004, which might provide some difficulty in interpretation although it is only a small proportion of the total and in any case its results (uppermost line in the above plot) are close to the median for the pooled analysis. The remaining comparators are all placebo groups.

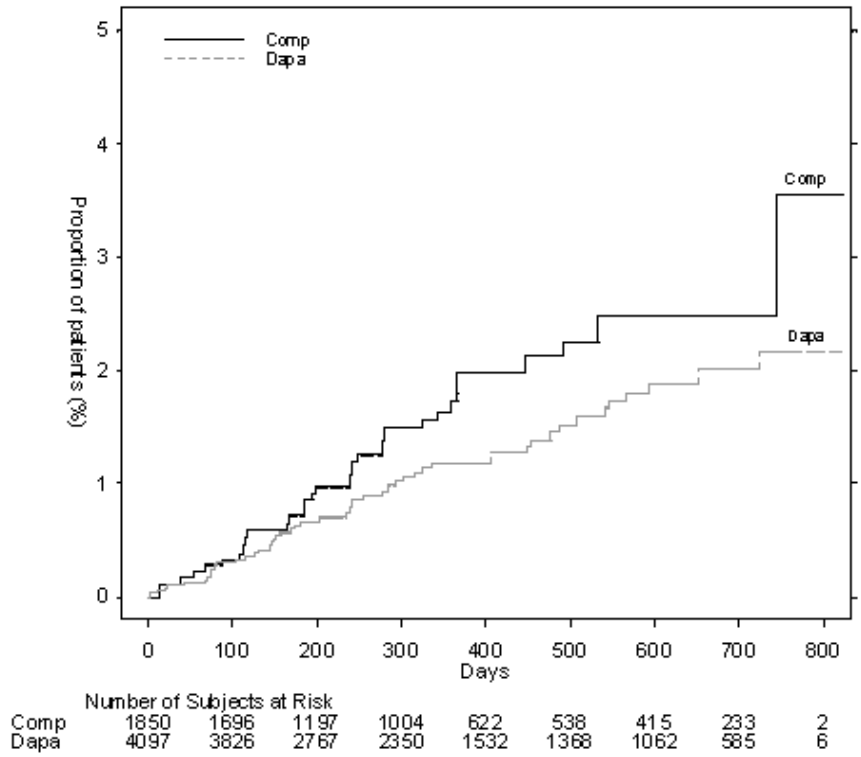
[42] Food and drug administration. Guidance for industry: diabetes mellitus – evaluation cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008

Figure 4. Forest plot of the hazard ratio and 95% CI from the meta analysis. Short term and long term period. Pooled analysis.



The overall event rate was 11.3 events/1000 subject years for the dapagliflozin (all doses) group, compared with 16.6 for the comparator group. A Kaplan-Meier plot of this comparison over time is shown below (Figure 5).

Figure 5. Kaplan-Meier plot



Although the sponsor makes no such claim at this stage, these data offer some prospect that in the long-term the glycaemic improvement achieved with dapagliflozin might be

associated with a *reduction* in cardiovascular risk, an outcome aspired to but not always achieved in using medications for T2DM.[43]

Cardiovascular risk-related data were collected routinely during the trials. There was an overall small mean increase in LDL cholesterol, offset by a parallel increase in HDL-cholesterol and a decrease in triglyceride. Minor reductions, rather than increases, in blood pressure were seen. The overall effect of this combination of findings on cardiovascular risk would be neutral or slightly negative, and is supportive of the findings of the cardiovascular event meta-analysis.

As a separate issue, electrocardiographic assessment of QTc interval[44] changes was carried out as a routine part of each clinical study and no change attributable to dapagliflozin was detected.

Osteoporosis

There is no doubt that dapagliflozin causes at least a transient increase in urinary calcium excretion and the potential impact of this on calcium and bone metabolism has caused the sponsors to collect relevant laboratory data in the course of the clinical pharmacology studies and subsequent clinical development program. Unfortunately it is not possible from the PD studies to determine whether there is a persistent increase in calcium excretion; these data are discussed and summarised above.

In the overall development program, no increase in fracture events was found. However, in Study MB 102029 carried out on renally impaired subjects, 10 fractures were reported in dapagliflozin treated subjects, 7 (8.2%) with 10 mg and 3 (3.6%) with 5 mg dapagliflozin and none with placebo. PTH rose more from baseline with dapagliflozin than with placebo. Pooled data for subjects with moderate renal dysfunction also showed PTH to increase from baseline to Week 24 by 1.1 pmol/L with 10 mg dapagliflozin compared with 0.26 pmol/L in the placebo group (sponsor's *Summary of Clinical Safety*; not tested statistically). These subjects would have an underlying mild degree of secondary hyperparathyroidism which could be amplified by calcium loss due to dapagliflozin if this were occurring. Detail of similar data on subjects with normal renal function could not be located, although the sponsor's *Clinical Overview* states that "mean changes in PTH tended to be slightly higher in the dapagliflozin groups". Overall, the available biochemical data tend to suggest some degree of increased calcium excretion with consequent secondary hyperparathyroidism. Even if relatively mild, this pathophysiological scenario would have the potential to cause increased bone loss in the long-term. The situation is analogous to that arising with loop diuretics such as frusemide which increase calcium in parallel with sodium excretion and are recognised as a risk factor for the development of osteoporosis.[45]

In summary, biochemical data suggest the possibility of a risk for the development of osteoporosis with dapagliflozin treatment, certainly in association with any degree of renal impairment and possibly for the treatment population at large. Recognising this, the sponsor states (sponsor's *Clinical Overview*) that *the* effect of dapagliflozin on bone

[43] Gerstein HC et al. (2008). Effects of intensive glucose lowering in type 2 diabetes. Action to Control Cardiovascular Risk in Diabetes Study Group, N Engl J Med. 358(24):2545

[44] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the *heart rate* (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

[45] Rejnmark L, Vestergaard P, Heickendorff L, Andreasen F, Mosekilde L (2006). Loop diuretics increase bone turnover and decrease BMD in osteopenic postmenopausal women: results from a randomized controlled study with bumetanide. J Bone Miner Res. 21(1):163.

mineral density is being evaluated in ongoing Study D169000012 which will perform dual energy x-ray absorptiometry (DEXA) on subjects at 50 and 102 weeks and the 50 week data will be available sometime in 2011.

Breast cancer

In routine clinical safety monitoring an apparent imbalance in the number of subjects diagnosed with breast cancer was observed between dapagliflozin treated (9/4287; 0.2% for the overall population, 0.4% for the female population) and comparator subjects (0/1941) (sponsor's *Clinical Overview*). The diagnosis was made on Study Day 6 and Study Day 39 in two of the subjects, which would make any connection with study medication unlikely; in the remainder, the diagnosis was made between 193 and 330 days after commencement of dapagliflozin medication (sponsor's *Summary of Clinical Safety*).

Given the high incidence of breast cancer in the population at large, the specific high risk and age group involved in these studies and the documented increased risk of breast cancer with T2DM[46], it is arguable that the discrepancy in these data is the absence of cases in the comparator group. A factor in the apparent discrepancy is that the length of observation in the comparator cases was less. The sponsor undertook an epidemiological report *"A Comparison of the Incidence of Breast Cancer in the Dapagliflozin Clinical Program with the Incidence of Breast Cancer in a Reference US Population"*, which is presented below. This employs surveillance epidemiology and end results (SEER) data[47] to provide age and gender specific incidence rates in the general population to which is applied an "adjustment factor" of 20% to incorporate the increased risk of breast cancer in patients with T2DM.[46] This enables the calculation of a standardized incidence ratio (SIR) for dapagliflozin treated female patients in the program, being the ratio of the observed number of cases to the expected number of cases. SEER is a program of the National Cancer Institute.

With this calculation, the total number of expected incident breast cancer cases among female patients exposed to dapagliflozin is 5.9 cases; 7.1 cases are expected after factoring in the 20% adjustment for patients with Type 2 diabetes. The total number of expected incident breast cancer cases among female patients exposed to comparator drug from the Phase IIb/III clinical trials is 2.4 cases; 2.9 cases are expected after adding the 20% adjustment. Assuming a Poisson distribution, one could expect to observe 0 to 6 cases if the true expected number is 3 cases. On the basis of this statistical approach, which appears sound, the observed distribution of breast cancer in the study population is within the bounds of chance observation. The sponsor nevertheless indicates that breast cancer will continue to be carefully monitored in ongoing studies.

Bladder cancer

Subsequent to the commencement of this evaluation, information was received regarding the identification of a cluster of cases of bladder cancer amongst the study population of the Phase III trials in the application. This took the form of a letter from the sponsor to the TGA dated 10 June 2011 with two accompanying documents: a presentation of the clinical details of 7 cases of diagnosed bladder cancer which had been unblinded; and a summary document dated 7 June 2011 with a response from the sponsor on this issue and information regarding 3 further cases of bladder cancer, 2 of whom had been receiving dapagliflozin therapy and 1 placebo. The composite information therefore now is that *9* cases of bladder cancer have been reported in dapagliflozin treated subjects with 4354

[46] Larsson SC, Mantzoros CS, Wolk A. (2007). Diabetes mellitus and risk of breast cancer: A meta-analysis. Int. J. Cancer 121; 856-862.

[47] Surveillance Research Program, NCI SEER*Stat software (www.seer.cancer.gov/seerstat)

patient-years of exposure versus 1 case in the group of comparator subjects with 1899 patient-years of exposure.

It is noted from the sponsor's response that nonclinical studies showed no evidence of development of bladder tumours in animal models given large doses of dapagliflozin. From all the information so far available, the following observations are made:

1. Given the mechanism of action of dapagliflozin, there is no *a priori* reason to expect a carcinogenic effect on the bladder. Glycosuria occurs frequently in diabetes of all types and there is no association between bladder cancer and diabetes.
2. Bladder cancer is known to be caused by urinary excretion of the products of chemical carcinogens arising from sources such as tobacco smoking or other environmental exposure. The latency between exposure and clinical presentation is measured in decades. If these cases are attributable to exposure of the bladder mucosa to a carcinogenic metabolite of dapagliflozin, the period of latency is extraordinarily short.
3. Of the 7 cases originally described, it is noted that in 4 the abnormality of haematuria was recorded at the time of study entry. It is highly likely that in these cases the bladder cancer was already present, although undiagnosed, prior to administration of study drug. In one case in particular, the diagnosis was made 43 days after study entry. If these cases are excluded, the comparative incidence data would now be 4/4354 patient-years on dapagliflozin and 1/1899 patient-years on comparator treatment.
4. A crude estimate of the likely incidence of bladder cancer in the study population can be made from the following: in 2010, 70,500 cases of bladder cancer were diagnosed in the USA population of 312 million.[48] This is the only regional information readily available. Cases rarely occur below the age of 50, so these cases could be taken as occurring within a population aged 50 and over, corresponding approximately to the demographic of the study population, which in the case of the USA totals approximately 150 million. This yields an incidence of bladder cancer, in the population aged >50 years, of 47 cases per 100,000 population per annum. Accepting this, the expectation from 4354 patient-years would be 2.05 cases and from 1899 patient-years would be 0.89 cases. The ratio of observed to expected cases is therefore approximately 2 for the dapagliflozin group and 1 for the comparator group. The question is whether this is outside the bounds of probability on chance alone. This would be clarified by a proper epidemiological assessment similar to that undertaken by the sponsor for the breast cancer cases discussed above.

Immunological events

None reported; no evidence of immunological pathology associated with this drug.

Safety related to drug-drug interactions and other interactions

Dapagliflozin has a low propensity for drug-drug interactions (see comments under *Pharmacokinetics*) and no safety issues related to this factor are anticipated or evident from the submitted data.

[48] Jemal A, Siegel R, Xu J, Ward E (2010). Cancer statistics. CA Cancer J Clin. 60(5):277

Discontinuation due to adverse events

Discontinuation due to AE was infrequent and occurred in between 2.5 and 3.2% of subjects in the various treatment groups including placebo. These subjects represent a small proportion of discontinuations. No discontinuations occurred for reasons which appear unusual or outside the overall spectrum of AE. In the placebo group, the most common reason for discontinuation was weight gain which might reflect subjects recruited to the study having an expectation of receiving a drug which helps weight loss. In the dapagliflozin treated subjects, the most common reason for discontinuation was a rise in serum creatinine which reflects the attention paid to this aspect of safety monitoring as outlined above. Other common reasons for discontinuation were related to genital and urinary tract infections, again as already discussed.

Postmarketing experience

No data exists, as the product is not yet marketed.

Evaluator's overall conclusions on clinical safety

Safety issues regarding this application mainly relate to areas of special interest which were identified by the sponsor early in the development program and which have been adequately addressed in the clinical trial protocols. Hypoglycaemia does not appear as a major safety concern with dapagliflozin. There is a significant incidence of genital and urinary tract infections attributable to the glycosuria which occurs as an essential part of dapagliflozin's mechanism of action. These are manageable risks. Potential adverse events related to hypovolaemia and hypotension can be addressed by attention to risk factors and avoidance of use of the medication if necessary; the sponsor recommends use of the lower 5 mg dosage in this situation. An *increase in haematocrit* appears to be an unavoidable side-effect of dapagliflozin but is of minor extent in almost all instances and not associated with morbidity in the studies carried out so far.

Dapagliflozin appears on good evidence to be free of any association with an increased incidence of cardiovascular events.

There is equivocal evidence of an increased risk for bone loss with the potential development of osteoporosis, which requires ongoing monitoring and this is recognised by the sponsor.

The safety of using dapagliflozin in a subgroup of patients with moderate renal dysfunction, those with eGFR ≥45 and <60 mL/min/1.73 m^2, is a point of contention for this evaluation as outlined above and is addressed in the risk/benefit discussion below.

The recent observation of clusters of breast cancer and bladder cancer cases in the dapagliflozin clinical study population is felt most likely to be a chance observation in each instance. Further epidemiological evidence is required regarding the bladder cancer cases.

Apart from these issues, tolerance of dapagliflozin by study subjects was good and its overall safety profile appears satisfactory.

List of questions

The following matters were drawn to the attention of the sponsor and in some cases assisted further assessment of the application.

Efficacy

The conclusions and recommendations (see below) regarding use of the 5 mg tablet and whether it should be registered, may require discussion with the sponsor. Otherwise, there are no questions.

Safety

The sponsors should be asked whether they feel that the risk/benefit equation for use of dapagliflozin has been adequately addressed specifically for subgroup 3A of patients with moderate renal dysfunction; those with eGFR ≥45 and <60 mL/min/1.73 m^2. As noted below, it is the opinion of this evaluator that this may not be so and that consideration should be given to advising that dapagliflozin should not be used in any patient with moderate or severe renal dysfunction (eGFR <60 mL/min/1.73 m^2).

1. The sponsors should be asked whether they would agree that a more definitive statement be made in the PI regarding the use of dapagliflozin in patients with severe hepatic impairment, rather than leaving it to the assessment of the prescriber.
2. While this evaluation has not specifically reviewed information about use in pregnancy, it is felt that as there are "*no adequate well-controlled studies of dapagliflozin in pregnant women*" and in view of the animal evidence of potential renal abnormalities in progeny, the sponsors could be asked whether a simple recommendation that dapagliflozin not be used in pregnancy might be more appropriate.

(1) Clinical summary and conclusions

Benefit risk assessment

Benefits

Beneficial effect of a therapeutic agent for the treatment of diabetes should ultimately be measured in terms of positive health outcomes which occur as a result of correction, usually partial, of the metabolic abnormalities of diabetes, particularly hyperglycaemia. These include improvements in symptoms and signs directly attributable to high blood glucose, such as thirst, polyuria, weight loss and propensity to infection; and in the longer term, reduction in the incidence of complications of diabetes including retinopathy, nephropathy, neuropathy and micro- and macrovascular disease. Whilst other factors are involved to a varying degree, there is now a wealth of evidence implicating blood glucose elevation, both fasting and post prandial, in the pathogenesis of these complications. In turn, HbA1c as an integrated measure of blood glucose over time, can be regarded as an index for long-term health outcomes; a reduced incidence of cardiovascular outcomes has been seen in association with lowering of HbA1c as a result of insulin treatment and some oral diabetes therapies[49], particularly metformin[50], although doubts have been raised about the benefit to risk ratio of more intensive therapy.[51]

[49] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352(9131):837 (1998)

[50]Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Arch Intern Med.169(6):616 (2009)

[51] Gerstein HC et al (2008). Effects of intensive glucose lowering in type 2 diabetes. Action to Control Cardiovascular Risk in Diabetes Study Group,. N Engl J Med. 358(24):2545.

A balanced conclusion from the above is that benefits, particularly long term benefits, are likely to follow from reduction of blood glucose irrespective of how that reduction is achieved. Dapagliflozin is shown by the data in the application to achieve improvements in blood glucose and HbA1c which are modest but of the same order as those achieved by other oral diabetes therapies, usually 0.5-1%. The limitation of improvement in HbA1c to this level is the reason these therapies often have to be used in combination.

A potential benefit associated with the blood glucose lowering action of dapagliflozin is that it is achieved without any interference with the synthesis or secretion of insulin, or modulation of intracellular events subsequent to receptor binding of insulin. Its pharmacodynamic target is simply the reabsorption of glucose in the renal tubule. It does not, on the basis of available information, act on enzyme systems with the potential to cause "off target" and possibly harmful effects unrelated to diabetes, such as may be the case for example with thiazolidinediones and DPP4 inhibitors.

A possible benefit is modest body weight reduction, averaging 2-3 kg; and perhaps more particularly, the avoidance of weight gain which is a frequent occurrence resulting from other diabetes treatments, particularly insulin, sulphonylureas and thiazolidinediones. Weight reduction is a major therapeutic goal for most patients with Type 2 diabetes. Metformin may assist with achieving this in some patients, although not as reliably as would seem to be indicated by the data for dapagliflozin. The only other diabetes therapies which help with weight reduction are the alpha glucosidase inhibitors (acarbose) and the injectable preparation exenatide.

Risks

The sponsor has maintained a comprehensive program of safety assessment throughout the development of this product and the list of identified and potential risks associated with dapagliflozin treatment referred to above corresponds closely with the independent assessment of this evaluation from the data provided. This evaluation has identified no additional risks beyond those already noted in the sponsor's RMP but there are some areas which require additional comment, as follows:

Calcium metabolism and bone density. For the reasons outlined in detail above, this evaluation has concluded that there is not only a hypothetical basis for anticipating the possibility of progressive bone loss for dapagliflozin therapy but a definite biochemical signal in the safety data that this may be occurring in at least some of the treated subjects. The sponsors appear to recognise this in having planned an ongoing study with measurements of DEXA and biochemical bone markers, although the risk management activity listed in the table, the information given in the PI and the general discussion of this issue in the study documentation suggests that they believe this problem to be restricted to renally impaired subjects. It may turn out to be a more widespread problem and if this should be so, early identification will be crucial. It is possible that that attention to dietary calcium intake, which is often deficient in the particular population at risk here, could form part of appropriate preventive management. In view of this, monitoring of bone density should in some way form part of ongoing pharmacovigilance.

Renal impairment: it is the conclusion of this evaluator that there is a level of risk associated with the administration of dapagliflozin to the particular subgroup of moderately renally impaired subjects with eGFR ≥45 and <60 which is not worth taking in view of the parallel reduction in efficacy sustained in this group.

No specific harm is seen as likely to arise from the chronic reduction in serum uric acid which occurs in dapagliflozin treated subjects but alertness to potential unexpected outcomes should form part of routine pharmacovigilance.

The clusters of cases of breast cancer and bladder cancer which have been identified and which are discussed above should be seen not so much as risks but as threats, as the

evidence available at this stage is consistent with these being chance observations in this large population of individuals who are in the age range susceptible to each of these conditions. Monitoring and review of the situation should continue to occur.

Balance

Excepting the conclusions made by this evaluator regarding moderately renally impaired subjects, the balance of likely benefit versus potential risk with administration of dapagliflozin 10 mg appears favourable. This evaluator would support the suggestion implied that monotherapy be restricted to patients in whom metformin is contraindicated or not tolerated. While "head to head" comparisons are restricted to a secondary outcome of Study MB 102008, the data from that study and other sources suggest dapagliflozin to have no greater efficacy than metformin[52] as monotherapy and in view of the long established safety record of metformin, at least in those for whom gastrointestinal tolerance has been established, it would seem inappropriate to use dapagliflozin in preference.

Use of the 5 mg tablet

The only proposed use of the 5 mg tablet is that covered by the following statement in the draft PI, in the section on dosage and administration:

"For patients at risk for volume depletion due to coexisting conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose of (dapagliflozin) may be appropriate".

With regard to this recommendation, the following observations are made:

1. No studies have been done which demonstrate that use of the 5 mg tablet in this loosely defined group results in an appropriate balance of efficacy and safety. The references given in the PI to back up the above statement include sections of the application which show that (a) the 10 mg dose is more efficacious than 5 mg (sponsor's *Clinical Overview*; (b) AE were less frequent with the 5 mg as opposed to 10 mg dose given to subjects receiving loop diuretics (sponsor's *Summary of Clinical Efficacy* and *Summary of Clinical Safety*). The number of incidents upon which this conclusion is based is very small, involving 2-5 subjects and the sponsor's *Summary of Clinical Efficacy* itself states that with regard to the interaction with loop diuretics there is only "limited experience". Another reference given is to the sponsor's *Clinical Overview* regarding events of hypovolaemia, hypotension and dehydration in subjects with moderate renal impairment; these occurred in 8.4% of 5 mg dosed subjects, 9.4% of 10 mg dosed subjects and 4.8% of placebo subjects.
2. While there is data demonstrating efficacy of the 5 mg dose (Study MB 102021), those studies in which both 5 mg and 10 mg doses have been used clearly show the 10 mg dose to be more efficacious and this is indeed the sponsor's own conclusion (sponsor's *Clinical Overview*).
3. The group of patients specified as being "at risk" is likely to include some with co morbidities including moderate renal dysfunction who are likely (as described elsewhere in this report) to be less responsive to dapagliflozin and accordingly derive less benefit.
4. The definition of the group at risk is so loose that the prescriber is likely to have difficulty determining to whom the 5 mg recommendation should apply.

[52] Sponsor comment: "Dapagliflozin was compared with metformin in Study 034: it was non-inferior to metformin in HbA1C and superior to metformin on FPG and WT."

5. The balance of benefits and risks associated with use of the 5 mg tablet are not addressed in the sponsor's risk management plan.

In summary, the sponsor is suggesting that a less effective dose of dapagliflozin be given to a poorly defined class of patients who are more likely to suffer adverse effects, possibly even with the reduced dosage, and who may in any case be less likely to respond to the medication. The recommendation that a 5 mg dosage "may be appropriate" is as the term suggests an assumption, not firmly based on evidence.

It is clear that the benefit to risk ratio for use of the 5 mg tablet in the only situation for which it is proposed is far less favourable than that which applies to the therapeutic uses proposed generally in the application.

This evaluator suggests that the clinical circumstances which the sponsor suggests as indications for the reduced 5 mg dose should be regarded as situations in which dapagliflozin is contraindicated, or at least not recommended. In general, it is felt that there are no grounds for recommending the use of the 5 mg dapagliflozin tablet.

Conclusions

Dapagliflozin 10 mg is suitable for registration under the conditions listed below. The use of the 5 mg tablet for the indications proposed is, on the basis of the evidence presented, not supported.

Recommended conditions for registration

Apart from the conditions suggested by this evaluator regarding safe use with moderate renal dysfunction, no barrier is seen to registration of the 10 mg tablet for any of the requested indications as the benefit/risk balance would seem equivalent for all the therapeutic situations involved. For the reasons given above, registration of the 5 mg tablet is not supported.

Long term safety monitoring should continue and should specifically involve vigilance for the development of osteoporosis.

Further epidemiological information should be sought regarding the significance attributable to the observation of cases of bladder cancer in the study population, and surveillance for such cases and any further cases of breast cancer should continue.

Second round clinical evaluation

The task of the second round clinical evaluation was to evaluate and provide comment upon the responses to questions and other additional information provided by the sponsors following the first round of the evaluation process which included a clinical evaluation report (CER) provided by this evaluator. That document, designated as the "first-round CER", will be referred to throughout this report.

This report responds to information provided by the sponsors under cover of a letter dated 26 October 2011. The contents of this response are reviewed and the areas requiring comment in this report highlighted. Another section comprises comments and responses on the specific matters indicated. Conclusions and recommendations are then presented.

Comments and responses

Question 1: Use in moderate renal dysfunction

It was recommended (first-round CER) that the advice that dapagliflozin not be used in patients with severe renal impairment be extended to those with moderate impairment (eGFR <60 mL/min/1.73m^2). It is noted that the sponsor has accepted this

recommendation and that appropriate changes have been made to the *Precautions* and *Dosage and administration* sections of the PI.

Question 2: Use with hepatic impairment

The issue raised here was in relation to the recommendation in the PI that *"the benefit: risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin has not been specifically studied in this population"*; an alternative was suggested (first-round CER) that a statement simply be made that dapagliflozin not be used in this population. In their response, the sponsors emphasise that there is no evidence of hepatic toxicity or adverse effect in relation to impaired liver function (see discussion below) and the sponsor suggests that it is reasonable to leave a decision about use of the medication to the prescriber on the basis of an individual risk/benefit assessment. This misses the point that there are two issues here. Firstly, there is the potential for adverse effects on the liver of using dapagliflozin in patients with normal hepatic function. This is well dealt with by the sponsors' response and is not seen by this evaluator as a hazard. The second and quite separate issue is that of using dapagliflozin in patients with established significantly abnormal hepatic function.

As quoted in the previous paragraph, it is the sponsors' own statement that the safety and efficacy of dapagliflozin has not been specifically studied in patients with severe hepatic impairment. With regard to efficacy, it is reasonable to speculate that the drug could be useful for the treatment of T2DM in this population as its action is not dependent on liver function. Nevertheless, in view of the effects of impaired liver function on carbohydrate metabolism this remains to be demonstrated. Furthermore, there is a specific potential safety concern in relation to the potential for hypoglycaemia. With increasing impairment of hepatic function, the management of T2DM becomes complicated by a reduction in fasting hyperglycaemia and an increase in post prandial glycaemia. These are natural consequences of the loss of the physiological role of the liver in blood glucose regulation. If liver function is sufficiently impaired to limit the capacity for hepatic glucose output in the fasting state, imposing a drain on the pool of fasting blood glucose via the mechanism of renal glycosuria as a consequence of dapagliflozin administration could potentially exceed the capacity of hepatic glucose output to compensate for this and hypoglycaemia might be the result. The possibility of this occurring in patients with impaired liver function is increased by the higher exposure demonstrated in PK Study MB 102027 of the original application (first-round CER). It is, again hypothetically, likely that the potential for hypoglycaemia would be further increased in the situation of co administration with a sulphonylurea which is one of the proposed indications. In the absence of clinical data to address these potential efficacy and safety issues, it appears unreasonable to suggest that dapagliflozin be used in such patients on the basis of an individual assessment by the prescriber.

It is also pointed out that current Australian prescribing advice is that glitazones are contraindicated in patients with impaired hepatic function, that metformin should only be used with caution and that significant precautions are advised with sulphonylureas (for example, gliclazide). All of these drugs are listed for co administration with dapagliflozin in the proposed indications. Limitations on these aspects of the indications will severely limit the potential application of dapagliflozin in this patient population.

It therefore remains the recommendation of this evaluation, as stated in the first-round CER that the drug should not be used in patients with severe hepatic impairment.

Question 3: Use in pregnancy

The first round CER recommendation was that as there are *"no adequate well-controlled studies of dapagliflozin in pregnant women"* and in view of the animal evidence of potential renal abnormalities in progeny the sponsors could be asked whether a simple

recommendation that dapagliflozin not be used in pregnancy might be more appropriate in the PI.

Bladder cancer update

The finding of an apparently increased incidence of cases of bladder cancer among study subjects receiving dapagliflozin was discussed in the first-round CER. This discussion was based not only on the original data submission but on the data referred to in the 10 June 2011 communication from the sponsor with TGA. The content of this latter communication is included amongst the updated information which forms the subject of this report. The sponsor has provided clinical data including any cases reported up to 16 September 2011 together with an extensive review of the literature and an epidemiological report. These data including the background literature information are not substantially different to those which were the basis for the discussion in the first-round CER. No further cases of bladder cancer have been reported, with the figures standing at 9 cases on dapagliflozin treatment and 1 case on comparator treatment. The overall exposure for the study population with the latest data cut-off[53] is given as 4977 patient years for the active drug population and 2348 for the control population, compared with the 4354 and 1899 patient years, respectively, quoted in the first-round CER.

Individual data for the 10 study subjects identified with bladder cancer is provided in Table 10 below.

The questions to be addressed here are whether there is any relationship between the incidence of these tumours and the dosage of medication used; whether there is any evidence of time dependency indicated by the interval between the start of medication and the time of diagnosis of the tumour; and whether it can be determined that the overall incidence rate of these tumours is or is not greater than expectation in the population at risk.

[53] Sponsor comment: "As of 16 September 2011".

Table 10. Summaries of confirmed malignant bladder cancer events, short term plus long term period as of 16 September 2011 ordered by study day within treatment group.

Age/Sex	Dapa Dose ± Treatment	Tumour type	Grade	TNM[a]	Diagnosis Study Day	Smoking Status	Baseline Haematuria	Haematuria within 6 m before Randomization	Haematuria after randomization
75/M	2.5 mg	Transitional cell	Grade 2	T2, N0, MX	43	Former	2+	YES	YES
48/M	Dapa 10	Transitional cell	Low grade Non-invasive	NA	74	Former	Negative	YES[c]	NO
67/M	5 mg + Pio	Transitional cell carcinoma	Grade 3	T2	144	Never	Trace	YES	YES
55/M	10 mg	Transitional cell	Grade 1 Non-invasive	NA	169	Current	Trace	TRACE	YES
63/M	5 mg + Ins	Transitional cell	Grade 2 Non-invasive	Ta	393[d]	Current	Negative	NO	YES[c]
67/M	10 mg + Ins	Transitional cell	Grade 2	NA	399	Never	3+	YES	YES
60/M	5 mg+ Met	Transitional cell	Low Grade Non-invasive	Ta, N0, M0	512	Former	2+	YES	YES
66/M	10 mg + Ins	Transitional cell	Low Grade Non-invasive	NA	581	Former	Negative	NO	YES
76/M	10 mg + Met[b]	Transitional cell, partial squamous differentiation	High Grade Invasive	T1 M0	727	Never	Negative	NO	YES
66/M	Comparator	Transitional cell	High grade Micro-invasive	M0	136	Current	3+	YES	YES

[a] TNM Classification of Malignant Tumours
[b] Patient started at 2.5 mg and titrated up to 5 mg and then 10 mg.
[c] Haematuria was established outside of the study.
[d] Tumour detected at Day 358, AE report at Day 393.
m = months; Pio = pioglitazone; Ins = insulin; Met = metformin; NA = not available.

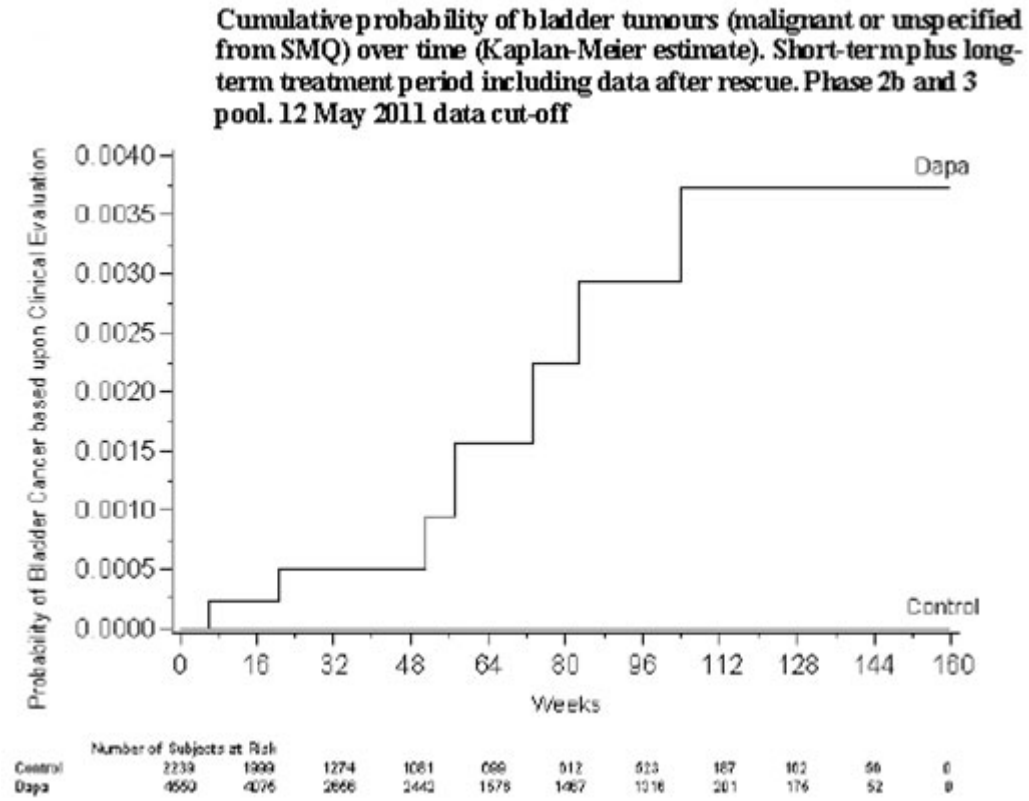
Dose dependency

Of the 9 cases in the above table, 4 (44%) had been taking 10 mg dapagliflozin (in 1 case, titrated up from a lower dose), 3 were on 5 mg and a single case was on 2.5 mg. The proportion on 10 mg (44%) is higher than the overall proportion of subjects in the clinical trial program taking the 10 mg dose (1193/4922, 28%; first-round CER) but this difference would be dependent on a distribution of 1-2 patients between the dosage groups and does not seem significant. While the data should continue to be monitored, there is no evidence at present of dose dependency amongst the diagnosed cases of bladder cancer, except of course for the difference in numbers of cases between those taking any dose of dapagliflozin (9) and no dose at all (1). This is discussed further below.

Time dependency

The dapagliflozin treated cases shown in Table 10 above are listed in order of the duration of their study medication at the time of diagnosis of bladder cancer. Column 6 of the table shows the day of the study when the diagnosis was made. It is evident that the cases appear at regular intervals from the start of the studies right through to the maximum of two years duration. This is graphically illustrated by the Kaplan-Meier graph below (Figure 6).

Figure 6. Kaplan Meier Plot



This graph was constructed with an earlier cut-off date than Table 10 when there were 7 dapagliflozin and no control cases. The two additional dapagliflozin cases were diagnosed at 21 and 24 weeks respectively and would have the effect of "smoothing out" the apparent step in the graph between 30 and 50 weeks. The data, limited though it is, suggests a constant rate of diagnosis of these cases over time from the commencement of the studies. A medication effect is not excluded by this observation but there is no evidence of a period of latency between the initiation of medication and the first appearance of the cases, which would constitute more powerful evidence.

Unfortunately, with only a single case diagnosed in the comparator group, it is not possible to compare the rate of appearance of cases between the treated and comparator groups.

Overall incidence of bladder cancer

Some comment is required regarding potential confounding factors in the individual bladder cancer cases. This is obtained from the sponsor's response. The cases are described as cases 1 to 9 in order that they appear in Table 10 above.

Case 1 was observed to have haematuria prior to randomisation and had continued positive urine blood results until the diagnosis of bladder cancer was made on Study Day 43. There would seem no doubt that his tumour was present prior to the commencement of study medication.

Case 2 showed no haematuria on screening but did give a history of renal stones and haematuria two years previously. On Day 74 of the study a computed tomography (CT) scan done for other reasons incidentally showed a bladder tumour which histologically was a non-invasive transitional cell carcinoma of low-grade. It is most unlikely that a tumour of that type sufficiently large to shown on a CT scan would develop within that timeframe.

Case 3 did show dipstick trace haematuria at screening but this was not confirmed on microscopy. The patient had been treated with 45 mg daily pioglitazone for 7 months prior to the commencement of the study. This is a potential confounding factor.

Case 4 also showed dipstick trace haematuria at screening and is described as having had intermittent haematuria for 3 months prior to diagnosis of a bladder cancer at Day 169. This would suggest that there was clinical evidence of abnormality by about Day 70.

Case 5, although diagnosed at Day 393, is recorded as having reported microscopic haematuria for 3 months beforehand. There is no objective confirmation of this.

Case 6, diagnosed at Day 399, showed haematuria at screening and throughout the study. The relevant paragraph from the case narratives reads as follows: "*Blood in urine (dipstick) was 1+ and 3+ at measurements before/at randomisation and then intermittently positive results during the study. Microscopy for red blood cells showed 31-50 rbc/hpf (day -13) and 0-5 rbc/hpf (day 1)*". There would appear little doubt that the bladder carcinoma was present at screening and it seems regrettable that the patient was commenced in the study without further investigation and continued for over a year before the diagnosis was made. Further comment on this matter is made towards the end of this section.

Case 7 presented at Day 509 with ureteric colic and had a stone in the right ureter. The low-grade bladder carcinoma was an incidental finding at cystoscopy. At screening, he had been dipstick positive (2+) for blood but subsequently negative on microscopy. Whether the haematuria at screening was definite or whether it related to the stone (of which there was no previous history) or the carcinoma, is conjectural.

Case 8 presented at Day 581 with gross painless haematuria. There had been no previous detection of haematuria.

Case 9 was diagnosed at Day 727. As in case 8, there had been no previous abnormality.

Case 10, a patient on comparator treatment, also had 3+ haematuria at baseline, followed by positive results through the study. Microscopy for red blood cells appears to have been positive on one of two samples prior to randomisation. The diagnosis of bladder carcinoma was made at Day 156.

In summary, in 3 cases (Cases 1, 6 and 10) it appears certain that the tumour was present before treatment was commenced. In 3 others (2, 3 and 4) there is a significant likelihood that this may have been the case. The remaining cases were all diagnosed in the second year of medication and a relationship to medication should be regarded as possible.

These data, particularly the presence of haematuria at baseline in 6 of the 10 subjects, reinforce the point made in the first-round CER that some, if not the majority, of these tumours may have been present prior to the initiation of study treatment. Based on the above observations, it appears that in certainly 2 and possibly 5 of the actively treated cases and in the 1 case on comparator treatment, the pathology was present prior to initiation of study medication. If for the sake of argument that proposition is accepted, we are left with between 4 and 7 bladder cancer cases detected while subjects were receiving active treatment compared with none on control. These figures together with the exposure data quoted above yield incidence values of 0.08 and 0.14/100 person-years for the dapagliflozin treated group and 0/100 person-years for the placebo group.

The essential question at issue is whether this level of bladder cancer incidence differs from expectation for the population at risk. In the first-round CER, a crude estimate of incidence of bladder cancer in the general population aged >50 years approximating 0.05/100 person-years was derived. It was suggested that the situation would be assisted if more reliable data could be derived from a proper epidemiological study. Such an assessment has now been provided by the sponsor with the current documentation. A relevant and apparently reliably referenced aspect of this review is that there may be an increased incidence of bladder cancer in subjects with T2DM, with a hazard ratio quoted

of 1.5 versus the non diabetic population. A consensus statement of the American Cancer Society and American Diabetes Association is also quoted, citing a risk ratio of 1.2-1.5 for this relationship. The population incidence for T2DM subjects might therefore be 0.07-0.08/100 person-years.

It is important to point out that there is a decimal point error in the figures quoted in the sponsor's clinical response in regard to the incidence of bladder cancer amongst T2DM patients on the Kaiser Permanente Northern California diabetes registry. An incidence rate of 68.8 cases per 100,000 person-years corresponds to 0.07/100 person-years, not 0.69 as stated (likewise, the figure quoted for pioglitazone treated patient should be 0.08, not 0.82/100 patient-years). Also, the figure quoted in the subsequent paragraph regarding the 861 cases detected in this clinical database should read that there was an unadjusted incidence rate of 0.45 per 100 patients *over 5 years*, which as stated corresponds to a value of 0.09/100 patient-years.

Given this background information, including the assumption of pre existing pathology in some of the subjects, it appears most likely that the number of bladder cases detected is consistent with epidemiological expectation. Undoubtedly, the conditions of the studies impose a detection bias, as urinalysis for blood is specified at each visit; for example, on each of the 13 visits over the 51 week period of Study D1690C00006. Whether the baseline positive cases are ruled in or ruled out of the above statistical calculations, the fact remains that they would likely have remained undetected were it not for enrolment in the study.

Taking a conservative expectation for bladder cancer in the study population as 0.08/100 person-years, the number of expected cases in the control group would be 1.52, without allowing for the detection bias which would equally apply to this as well as to the actively treated group. The single case identified amongst comparator subjects (in Study D1690C00006) was diagnosed as a result of study procedures and otherwise may have remained undetected. It is difficult to postulate anything other than statistical chance to explain why 1-2 more cases have not been detected amongst comparator subjects.

It is also implicit from the above that the apparent incidence of bladder cancer in the study population may have been exaggerated by failure of the investigators to exclude pre existing cases. The study protocol for D1690C00006 specifies that amongst the procedures to be undertaken at both visit 1 and visit 2 (2 weeks prior to and on the day of randomisation) include urinalysis for blood by dipstick, with microscopy to be undertaken if the test is positive. Similar provisions appear in the protocols for other studies in the application. Exclusion criterion 12 to be applied at the randomisation visit, at least for Study D1690C00006 in which Case 6 cited above was a participant, was *"any clinically significant abnormality identified on physical examination, ECG or laboratory tests, which in the judgement of the investigator would compromise the subject safety or successful participation in the clinical study"*. While the exclusion criteria for some of the other studies are less specific, the failure to further investigate haematuria before proceeding with the enrolment of a subject in a study involving the administration of a renally active drug appears questionable.

Overall, the newly provided data do not alter and if anything strengthen the conclusion of the first-round CER that the numerical difference in incidence of bladder cancer cases between the active and placebo control groups is most likely due to statistical chance. Nevertheless, it must also be recognised that an effect of dapagliflozin on bladder cancer incidence cannot be excluded on valid statistical grounds and that a firm conclusion on this matter is not possible at this stage but might be achieved by further long term monitoring.

Breast cancer update

The sponsor's clinical response contains a similar spectrum of updated clinical data and background epidemiological information to that of the bladder cancer issue.

Most of this information was available to the first round CER, in which the incident cases of breast cancer in the study population is discussed with respect to the population-at-risk (see above).

By comparison with the data available at the time of writing the first-round CER (August 2011), there has been some evening out of the distribution of cases which at that time stood at 9 in the actively treated group by comparison with none in the control group; as of 16 September 2011 these figures are 10 and 3 respectively. At the 12 May 2011 data cut-off point, total exposure in the female study population was 1979 patient-years for dapagliflozin and 876 for comparator subjects. Based on these figures, the annual incidence of breast cancer calculates as 0.51/100 person-years for the dapagliflozin group and 0.34/100 person-years for the comparator group. These figures are a slight overestimate as they should be based on September 2011 exposure data which would be a little greater. The difference between the two groups has diminished with the increasing period of observation, as might be anticipated.

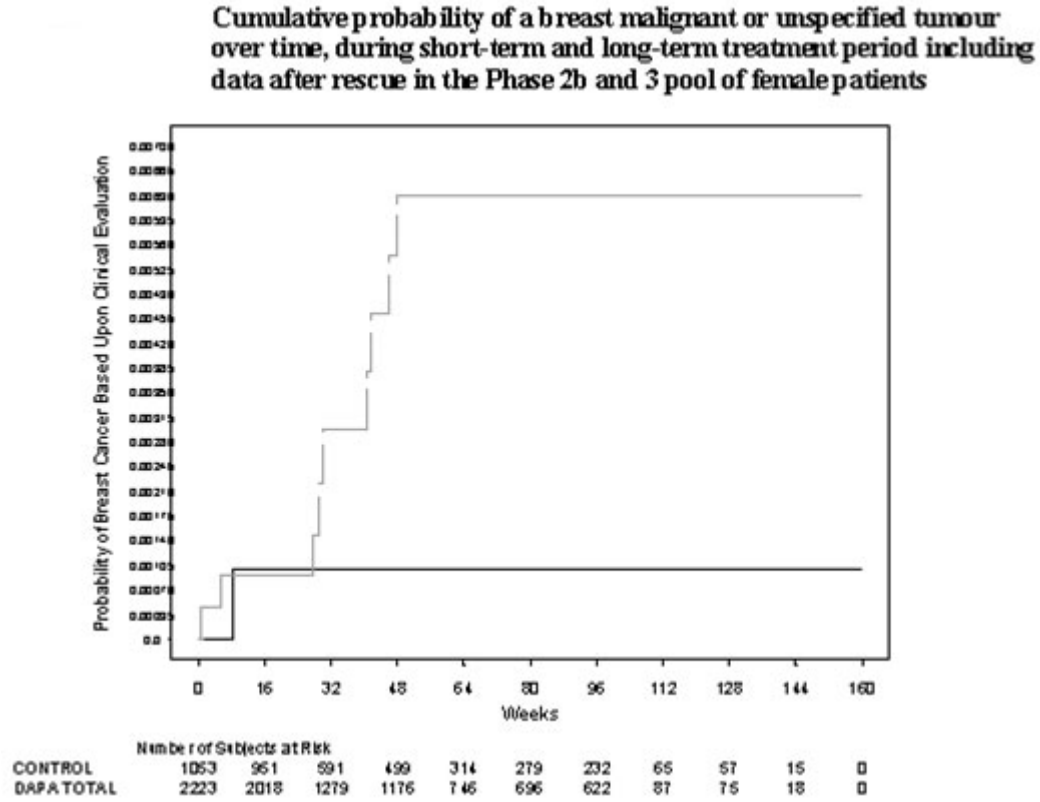
Dose dependency

Of the 10 dapagliflozin treated cases detected up until 16 September 2011, 6 were on the 10 mg dose, 1 on 5 mg and 3 on 2.5 mg. The proportion on 10 mg (60%) is double what would be expected assuming that there is no gender bias in the distribution of study drug doses. As with the bladder cancer cases, this apparent excess of 10 mg treated subjects is dependent on 2-3 cases and, although not statistically tested in the process of this evaluation, would seem unlikely to achieve significance. Nevertheless, this possible signal should be watched in further monitoring.

Time dependency

The time dependency of breast cancer discovery in relation to duration of study medication is illustrated by the Kaplan-Meier graph below (Figure 7).

Figure 7.



Note that the subject numbers are lower than for the bladder cancer data, as these data refer to the female study population only. As for the bladder cancer data, there is no evidence of latency between the commencement of study drug and case discovery.

In relation to breast cancer, the individual patient data have not been scrutinised for further relevant information as in this case there is no "tell-tale" observation as there is with haematuria in relation to bladder cancer.

Comparison of the figures with population reference data is difficult in view of the known effect on breast cancer incidence of age and co morbidities including obesity and T2DM. In their review of the epidemiological literature, the sponsors refers to, as they did in the original submission, the surveillance epidemiology and end results (SEER) program of the US cancer registry, quoting incidence rates in the general female population of 0.12/100 person-years for all females and 0.29 for females between the ages of 45 and 79 years. A French study on T2DM subjects is quoted as showing 0.25/100 person-years. Reference is again made to the Kaiser Permanente Northern California diabetes registry but again there is an error in the calculation which does not take account of the number of cases being over five years, and quotes an incidence rate of 0.618/100 patient-years; this figure should be 0.12/100 patient-years.

The best benchmark for comparison with the number of observed breast cancer cases in the dapagliflozin treated group will undoubtedly be the comparator group in the sponsor's own study data, particularly as detection bias is again a factor in these study participants who are subject to more intensive surveillance. In this context, the narrowing of the gap in breast cancer incidence between the active and comparator groups is somewhat reassuring although the number of cases is still small. As with the bladder cancer issue, the question of *a* possible association between dapagliflozin administration and breast cancer incidence can neither be confirmed nor excluded with the data so far available and will need, as suggested in the first round CER and indeed the sponsor's own risk management plan, to be the subject of ongoing monitoring.

Hepatic safety update

As noted in the first-round CER, there was no evidence of a systematic difference between active and comparator groups in liver function test abnormalities but there was a single case of acute hepatitis in which the question of relationship to dapagliflozin was raised, leading to the sponsor identifying the possibility of drug induced hepatitis as a potential risk requiring further monitoring. The sponsor's report identifies 54 cases of liver function test abnormality (mostly minor) which were reviewed by an independent hepatic adjudication committee. The distribution of the cases between active and control treatment (35-17, plus 2 still blinded) is consistent with the number of subjects in the respective groups. There have been no further severe cases similar to the one reported in the original submission.

A specific study (MB102104) is being undertaken to assess episodes of liver failure possibly occurring on dapagliflozin treatment.

Study MB 102059

The correction in this study report concerns the statistical methodology used for presenting the mean, standard error and 90% CI for dapagliflozin in this absolute bioavailability study. The study was evaluated in the first-round CER but this statistical issue was not raised by this evaluator. The correction does not appear to influence the results or clinical implications of the study.

Study D1690C00012

It was a conclusion of the first-round CER that biochemical data related to calcium metabolism indicated a potential risk of the development of osteoporosis in dapagliflozin treated subjects and that the sponsor recognised this and was undertaking monitoring of bone mineral density by DEXA in Study D1690C00012, the 24 week report of which was evaluated. The 50 week report of this study is now presented with the sponsor's response and reports bone density data before and at the completion of 50 weeks treatment in the two treatment groups (dapagliflozin plus metformin, and placebo plus metformin) of about 90 subjects each. The group data showed no significant change from baseline in any of the regions measured (lumbar spine, femoral neck and total hip) or any difference between the treatment groups. The mean change from baseline in both groups was <0.5%. 7/89 dapagliflozin and 4/91 comparator subjects showed a decrease of 5% or more; an observe change of this magnitude in <10% of the subjects is not surprising given the variability of the method.

This finding is reassuring but the time interval of one year is short in the context of bone density change and ongoing monitoring of bone density remains necessary. This issue was also the subject of questions in the request for further information from the sponsor. The sponsor's response includes proposals for a further extension including 2 year BMD measurements in Study D1690C00012, as well as a pharmacoepidemiological study of fractures in subjects taking dapagliflozin, detailed in the RMP and evaluation of fractures in a proposed cardiovascular outcomes study.

(2) Clinical summary and conclusions

It is noted that the sponsor's response contains no data or comments counter to the argument presented in the first-round CER that there was little basis for the use of the 5 mg tablet. The argument presented was that a positive benefit/risk ratio was less demonstrable for the use of a less effective dose in a subpopulation of subjects who were likely to be less responsive and also perhaps at more risk, for example of dehydration. Whilst acknowledging that the sponsor was not arguing for use of a reduced dose in the subgroup of patients with moderate renal dysfunction, the agreement (see above) to remove this group further weakens the case for use of the 5 mg tablet and it remains the

conclusion of this evaluator, as stated previously, that there are no grounds for recommending the use of the 5 mg dapagliflozin tablet.

Further information on the bladder cancer and breast cancer issues may ultimately need expert statistical evaluation, but tend to impact the safety profile of dapagliflozin positively although as outlined above is not felt that a firm conclusion can yet be made on either of these issues. The sponsor's proposed changes to the PI and RMP on these issues are supported.

Apart from the above reservations, the sponsor's response was seen as satisfactory in relation to the questions and issues raised in the first-round CER and the recommendation that the product (at least the 10 mg tablet) be registered was maintained.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 11.

Table 11. Ongoing Safety Concerns

Important Identified Risks	Genital Infections
	Urinary Tract Infections
Important Potential Risks	Hypoglycemia
	Volume Depletion
	Clinical Consequences of Increased Haematocrit
	Renal Impairment/Failure
	Bone Fracture
	Liver Injury
	Bladder cancer*
	Breast cancer*
Important Missing/Limited Information	Paediatric Population

	Pregnancy and Lactation
	Data in ethnic groups
	Elderly (>75 years)
	Severe renal impairment
	Moderate and severe hepatic impairment
	Congestive heart failure defined as New York Heart Association (NYHA) class III and IV

*newly added risks in updated RMP version 2.1.

OPR reviewer comment

The risk of progressive bone loss identified by the clinical evaluator is captured in the RMP under the potential risk of 'bone fracture' and is based on changes in bone resorption markers during the clinical program. The FDA's Endocrinologic and Metabolic Drugs Advisory Committee discussed clusters of breast and bladder cancer cases and both of these safety concerns have been added as Important potential risks in the summary table of Ongoing Safety Concerns in the updated RMP version 2.1 submitted in response to a request for information. The proposed pharmacovigilance and risk minimisation activities relevant to breast and bladder cancers are discussed in the following sections. The above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities are intended to continue to monitor all safety concerns. This will be supplemented by:

- targeted questionnaires for serious spontaneous reports of genital and urinary tract infections, renal impairment/failure, liver injury, bladder cancer and breast cancer, and
- case report forms from ongoing clinical studies for cases of genital and urinary tract infections, hypoglycaemia and liver injury.

At the time of this AusPAR, there were several ongoing studies which would continue to inform various safety concerns. These are briefly identified below (Table 12).

Table 12. Ongoing studies. Table continued across two pages.

Safety concerns	
Urinary tract infections (UTIs)	Study D1690C00019 is collecting data on approximately 400 subjects to evaluate asymptomatic bacteriuria, with preliminary results for 24 week follow up potentially available in fourth quarter of 2011.
Clinical consequences of increased haematocrit	· Studies D1690C00018 and D1690C00019 are collecting data from subjects who are at higher risk of cardiovascular events (arterial and venous events). The results from 24-week data are expected in fourth quarter of 2011, and the 52-week data is expected in second quarter of 2012. · *Study MB102029 includes long term extension period. · *Study D1690C00006 includes long term extension period.

Renal impairment/failure	· *Study MB102035 is measuring change in GFR over 12 weeks in dapagliflozin-treated or dapagliflozin+hydrochlorotiazide-treated groups, with a sub-study evaluating measured erythropoietin and plasma volume. · Study MB102029 for evaluating the effects of dapagliflozin and metformin combination in subjects, including those with moderate renal impairment. This study has a long term extension period and the 104-week data is expected in fourth quarter of 2011. · Study D1690C00006 for evaluating the effects of dapagliflozin and insulin combination in subjects, including those with moderate renal impairment. This study has a long term extension period.
Bone fracture	Study D1690C00012 is a 24-week Phase III study with a 78-week extension period to evaluate the effects of dapagliflozin and metformin combination on body weight. A sub-study of approximately 70 subjects will be evaluated by dual energy x-ray absorptiometry (DXA) for measuring bone mineral density (BMD) at lumbar spine (L1-4), femoral neck and total hip, with results available in second quarter 2012. Some of the information indicates the biochemical markers of bone formation and bone resorption will also be studied, with further details provided on 26 October 2011 in the response to the s31 request for information (s31 response –clinical, pp.47-60) which are as summarised below: · BMD measurement by DXA is used to establish whether dapagliflozin is associated with a mechanistic increase in fracture risk · bone formation and resorption biochemical marker measurements from serum/urine are used to inform the rate of bone turnover · two future studies are proposed in the updated RMP to investigate bone fracture as a safety objective · 182 randomised subjects and completion rate at the 50-week study period for BMD: n=81 dapagliflozin+metformin, n=83 placebo+metformin; for biochemical markers: n=78-80 dapagliflozin+metformin, n=76-80 placebo+metformin · BMD was measured by DXA at baseline, weeks 50 and 102 of treatment in lumbar spine (L1-4), femoral neck and total hip · A clinically relevant difference for BMD is determined to be a 2% change between baseline and week 50 measurements (for 50-week study end point) · Bone formation markers used in this study: serum osteocalcin, bone-specific alkaline phosphatase and procollagen type-1 N-terminal propeptide (P1NP) · Bone resorption markers used in this study: serum and urine C-terminal cross-linking telopeptides of type I collagen (CTX) and N-terminal cross-linking telopeptides of type I collagen (NTX) · Due to large variability in these markers, a change of at least 30% in bone resorption marker and 40% in bone formation marker is used to determine a biological effect based on a publication[54]
Elderly population	Studies D1690C00018 and D1690C00019 are collecting data from subjects

[54] Brown JP, Albert C, Nassar BA, Adachi JD, Cole D, *et al*. Bone turnover markers in the management of postmenopausal osteoporosis. *Clinical Biochemistry* 2009; 42(10): 929-942.

	stratified for 40% at ≥ 65 years old
Congestive heart failure (CHF) defined as NYHA	D1690C00018 and D1690C00019 are collecting data from subjects who are at higher risk of cardiovascular events, including those with CHF and NYHA class III.

*These studies were not specifically identified as planned pharmacovigilance activities for the indicated safety concerns in Tables 2.2 or 2.3 (Planned PV actions), but are included as pharmacovigilance activities for the indicated safety concerns in Table 5 (Summary of Risk Management Plan) of RMP version 2.1.

The following are planned post authorisation studies:

- Pharmacoepidemiology programs[55]:
  - Four programs to continue to monitor acute renal injury, acute hepatic injury, severe complications of urinary tract infections, breast cancer and bladder cancer in a larger population.
  - Prospective cohort studies that will be continuing over 5 to 10 years (10 years for the cancer program) after regulatory approval and utilising databases in the EU and US.
  - Data analysis is for non cancer outcomes planned at 18 months after initial market launch and at every 18 months intervals thereafter with final analysis planned at 60 months after market launch.
  - Data analysis for cancer outcomes is planned at 24 months after initial market launch and at every 24 month intervals thereafter with final analysis planned at 120 months after market launch
  - Patients with T2DM of ≥ 18 years who are new initiators (no exposure within last 180 days) of dapagliflozin or other antidiabetic drugs (ADs) other than SGLT2 inhibitors , insulin , metformin monotherapy, or sulfonylurea monotherapy and do not have a record for the relevant study outcome (within last 180 days) will be followed from the index date (date of first new drug prescription/dispense) until any study end-point, the end of study data or study period, the end of the risk window for the index AD, or the occurrence of any of the exclusion criteria, whichever occurs first. Discontinuation will be defined as no further prescription 30 or more days after the last prescription's days' supply. Follow-up will not be censored if other ADs are prescribed in addition to dapagliflozin or the comparator AD after the index date. For most patients, the risk window will end 60 days after the start of the last prescription (assuming the last prescription was a 30-day supply) for the index AD.. These criteria apply for all programs unless specified in the protocol..
  - Patients with any diagnosis of type 1 diabetes before cohort entry or first recorded AD is insulin monotherapy are excluded from the studies. . These criteria apply for all programs unless specified.
  - For each dapagliflozin initiator within each database, approximately four AD initiators will be frequency matched on 5-10 year age categories, sex, geographic region and calendar year of index date. .
  - A subset of identified cases of study outcomes will be validated via medical record review to determine the positive predictive value of the code-based case definitions in the databases.

[55] Sponsor amended this section of the AusPAR to further describe their planned studies.

  - For each of the studies, a draft study protocol/synopsis has been provided in response to a TGA request for information.

- A cardiovascular (CV) outcomes study, Study D1693C00001. A synopsis provided in response to a TGA request for information.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The proposed pharmacovigilance plan is not adequate as there is currently no agreed upon postmarket surveillance for Australia in the event that this drug is not approved in either the EU or US as discussed below:

- There is a lack of a contingency plan for all of the proposed post authorisation pharmaco-epidemiology studies in the event that the drug is not approved in both the EU and US as the databases intended to be used for the studies are based in the EU and/or US. The response to a TGA request for information has indicated that:

  "If US databases (but not EU) are available, we will utilize multiple US databases to complete the studies.....If EU (but not US databases) are available, we will determine the feasibility of executing the studies in databases outside of the US, such as Canada. In addition, we will consider alternative pharmacovigilance strategies (such as monitoring events in the proposed CV outcomes trial, as needed). If databases in both the US and EU are not available, we will need to re-evaluate our proposed RMP."

- There is no specific information provided on where the planned post authorisation D1693C00001 cardiovascular (CV) outcomes study will be conducted other than "*sites throughout the world*". It is assumed that this study will be conducted primarily in EU or US and no information is provided as to what the contingency plan is in the event that this drug is not approved in the EU and US.

There are also several notable issues relating to the proposed post authorisation studies as indicated below:

- It is noted that the exclusion criteria for the draft protocol for MB102122 ST study to assess the risk of bone fracture provided in response to a TGA request for information does not include a history of prior bone fracture events (within 180 days before index date) (RMP). It is unclear why subjects with a history of prior bone fractures are not excluded from the study considering bone fracture is the primary study outcome and that it has been reported that a prior history of fracture is associated with a significant increase in risk of subsequent fractures[56].

- The study outcomes of the proposed pharmaco-epidemiology studies are restricted to severe complications or hospitalisation/emergency room visits due to UTIs, renal failure, hepatic failure and bone fractures and will be unlikely to capture less severe events that do not result in hospitalisation/emergency room visits. This will not be adequate to provide a comprehensive evaluation of the risks relevant to safety concerns UTIs, renal failure, hepatic failure and bone fractures. It is noted that the planned clinical trial, cardiovascular outcomes Study D1693C00001 includes a secondary safety study outcome to monitor safety concerns including bladder cancer, breast cancer, liver injury, bone fractures, UTIs, genital infections and renal abnormalities that should have the capacity to monitor these events more comprehensively. However, it is unclear whether Study D1693C00001 will be sufficiently powered to detect all of the secondary safety study outcomes if the number of proposed participants is not reached as a result of this drug not being approved in the EU or US.

[56] Kanis JA, Johnell O, De Laet D., Johansson H. Oden A *et al*. A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 2004; 35(2): 375-382.

The RMP does not include a pharmacovigilance plan for the Ongoing Safety Concern "data in ethnic groups" (Missing information) and no justification was provided. If no adequate justification can be provided, an acceptable and adequate pharmacovigilance plan should be provided.

Risk minimisation activities

The sponsor has indicated that routine risk minimisation activities will be sufficient to manage all safety concerns.

OPR reviewer comment:

This was generally considered as acceptable. However, as dapagliflozin is the first-in-class drug to treat T2DM with a unique mechanism of action and associated adverse effects, the benefits of additional risk minimisation activities such as targeted health care professional and consumer education programs and/or materials may be considered.

Summary of recommendations

Pending the finalisation of the Clinical Evaluation Report, the OPR offers the conclusion based on the currently available information that the submitted RMP is not adequate to monitor the Ongoing Safety Concerns such as breast cancer, bladder cancer, urinary tract infections (UTIs), renal failure, hepatic failure and bone fractures during the postmarket period, for the following reasons:

- there was no assurance provided as to the implementation of the planned postauthorisation pharmaco-epidemiology programs to monitor these safety concerns if the drug is not approved in either the EU or US. The databases intended to be used for these studies are based in the EU and/or US. The sponsor has not provided an adequate contingency plan for implementing these studies if the drug is not approved in either the EU or US.
- It was unclear where the planned post authorisation D1693C00001 cardiovascular (CV) outcomes study will be conducted. This study will include a secondary safety outcome to monitor these safety concerns. If this will be conducted in the EU or US, the sponsor has not provided an assurance or an alternative plan to implement this study in the event that this drug is not approved in either the EU or US.

However, advice was sought from ACSOM to determine:

- an appropriate interim plan to implement in Australia if approvals in either the EU or US are delayed, and
- an appropriate plan to implement in Australia if there is no approval in either the EU or US.

The OPR recommended that the Delegate strongly considers the need for a post market surveillance plan, particularly for risks of breast cancer, bladder cancer, urinary tract infections (UTIs), renal failure, hepatic failure and bone fractures prior to registration. It was recommended that the Delegate give particular consideration to the adequacy of the proposed plan in the event that registration is delayed or not approved in either the EU or US.

If this application was to be approved it was recommended to the Delegate that the implementation of a RMP agreed upon by the OPR prior to registration, is imposed as a condition of registration.

The OPR also recommended that the Delegate considered information relating to the adequacy of the pharmacovigilance and risk minimisation activities of the RMP, which may also be referred to ACSOM for additional advice.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluator describes dapagliflozin as a synthetic aryl glycoside. The molecule is chiral, present as a single enantiomer. Dapagliflozin is present as a solvate with 1,2-Propanediol (which is also known as propylene glycol), in a crystalline form. The 5 mg and 10 mg (as dapagliflozin) tablets are immediate release, film-coated tablets with conventional formulations.

Bioavailability

Three bioequivalence studies were evaluated by the quality evaluator. They were of acceptable design and execution.

1. *Study No. 102059*: an absolute bioavailability study, conducted in seven healthy fasted adult males (Caucasians with a mean age of 26 years and a mean BMI of 24.3 Kg/m2) that used a ^{14}C-dapagliflozin intravenously infused microdose given almost simultaneously with an oral 10 mg tablet dose. Absolute bioavailability was suggested to be about 78% (90% CI 73.2, 82.8). The evaluator remarked, "The volume of distribution of dapagliflozin, mean Vss, following an intravenous administration was calculated as 188 L, which is greater than plasma volume, indicating extravascular distribution[57]. The geometric mean clearance of dapagliflozin following intravenous administration was calculated to be 207 mL/min, which is substantially less the plasma flow to either the liver or kidney in healthy subjects, indicating hepatic or renal extraction is low."
2. *Study MB102019*: a study that examined the effect of food on the bioavailability of the 10mg tablet, using an open label, randomized, 2-period, 2-treatment, crossover design, in 14 healthy male (n=13) and female (n=1) subjects. 6 subjects were Caucasian, 7 black and 1 Asian. The mean age was 34 years (range 24 years to 45 years); the mean BMI was 25.6 Kg/m^2.
3. A high fat meal decreased C_{max} of dapagliflozin and its inactive 3-O-glucuronide metabolite by 31% and 43%, respectively (and delayed T_{max} by about 1 h) but did not significantly alter the extent of absorption.
4. *Study MB102062*: this study is of pharmaceutical interest. It examined the bioequivalence of a heat-stressed (50°C at ambient humidity for 6 weeks) 10 mg tablet formulation, that is, comparing dapagliflozin as converted from the crystalline (dapagliflozin propanediol monohydrate) to an amorphous form. It was of an open label, randomized, 3-period, 3-treatment, 3-way crossover design, conducted in fasted and fed healthy subjects (n=29 of which 28 completed).

The results are shown below, including effects noted with Study MB102019 (Table 13).

[57] Dapagliflozin is also bound to plasma proteins. See nonclinical evaluation report.

Table 13. Results from Study MB102062

Parameter	Treatment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means and 90% CI of the Ratio (B/A or C/B)
AUC_{0-t} (ng.hr/mL)	Non heat-stressed fasting (A)	28	636.66	-
	Heat-stressed fasting (B)	29	**629.11**	**0.988 (0.958, 1.018)**
	Heat-stressed fed (C)	29	604.32	0.960 (0.932, 0.989)
$AUC_{0-\infty}$ (ng.hr/mL)	Non heat-stressed fasting (A)	28	662.85	-
	Heat-stressed fasting (B)	28	656.24	0.990 (0.959, 1.021)
	Heat-stressed fed (C)	28	638.47	0.972 (0.943, 1.003)
C_{max} (ng.hr/mL)	Non heat-stressed fasting (A)	28	172.65	-
	Heat-stressed fasting (B)	29	175.68	1.017 (0.922, 1.122)
	Heat-stressed fed (C)	29	96.61	0.549 (0.499, 0.605)
T_{max} (hr) Median (max, min)	Non heat-stressed fasting (A)	28	1.00 (0.75, 2.00)	-
	Heat-stressed fasting (B)	29	0.75 (0.50, 1.50)	-
	Heat-stressed fed (C)	29	2.00 (0.75, 4.00)	-
$t_{½}$ (hr) Mean (SD)	Non heat-stressed fasting (A)	28	11.6 (3.5)	-
	Heat-stressed fasting (B)	29	13.1 (4.2)	-
	Heat-stressed fed (C)	29	13.2 (3.8)	-

A similar study was conducted on a 2.5mg tablet and the results were consistent with the above and were dose-proportional.

No specific bioequivalence studies were done on the 5 mg tablet in relation to the 10 mg tablet. In respect of pharmaceutical aspects, the evaluator has accepted the justification for this omission.

Registration is recommended with respect to chemistry and pharmaceutical aspects.

Nonclinical

The nonclinical evaluator found that the overall quality of the submitted dossier was high, with all pivotal toxicity studies conducted under GLP conditions and using the proposed clinical route (PO).

Primary pharmacology studies, showing a reduction in plasma glucose levels and an improvement in insulin sensitivity, support the drug's use for the proposed indication. No clinically significant off-target activities are predicted based on secondary pharmacology studies. That is, dapagliflozin is highly selective for SGLT2 with nanomolar potency and with no effect on insulin levels in the species that were studied.

The pharmacokinetic s of dapagliflozin were generally similar in the species studied, including humans. It was orally bioavailable in most species (78-84%); plasma protein binding by dapagliflozin was high in animals and humans (89-95%) and concentration independent. Tissue distribution of dapagliflozin and/or its metabolites in rats was widespread. Unchanged dapagliflozin was the main circulating drug related compound in animal species, while both dapagliflozin and the UGT1A9-derived [inactive] metabolite dapagliflozin 3-O-glucuronide were the main drug related compounds in human plasma.

Dapagliflozin is not expected to alter the pharmacokinetics of co administered drugs via human CYP450 isozyme interactions. As dapagliflozin is chiefly metabolised by UGT1A9, inhibitors or inducers of UGT1A9 may affect the plasma kinetics of dapagliflozin.

In vitro binding studies indicated no unexpected off target adverse effects: there was no significant inhibition (≤33%) of radioligand binding at approximately 40 different receptors, enzymes and ion channels at dapagliflozin concentrations of at least 10 μM. Specialised safety pharmacology studies covered the cardiovascular system, while potential effects on the CNS, respiratory and renal systems were examined in toxicity studies. Dapagliflozin had a low order of acute oral toxicity in mice, rats and dogs.

No treatment related increase in tumour incidence was observed in mice or rats in 2 year oral carcinogenicity studies. However, the exposure to the metabolite dapagliflozin 3-O-glucuronide was similar to or below that expected clinically. The overall weight of evidence from test conducted *in vitro* and *in vivo* indicates that dapagliflozin is unlikely to be genotoxic. Adverse effects on fertility were seen in male rats.

Of note for potential human adverse effects:

- Dapagliflozin had an osmotic diuretic effect in all species and at all doses tested, and induced an increase in food and water consumption. Signs of dehydration and metabolic ketoacidosis were only seen at high doses in dapagliflozin-treated diabetic rats and in conjunction with decreased food and water intake. Increased urine output and glycosuria indicate a risk for dehydration and ketosis in diabetic patients. Hypercalciuria and natriuresis were also seen.
- Reduced body weight gain was occasionally seen.
- Urinary tract infections or histopathological changes consistent with urinary tract infection were observed in dapagliflozin-treated rats and dogs.
- A dose related increase in severity of chronic progressive nephropathy was seen in male rats treated for 2 years (at ≥8 times the clinical AUC). This may be of increased relevance in humans given the dependency of humans on the renal route of elimination.
- An increased incidence of irreversible renal pelvic dilatation was seen in the offspring of rats treated with dapagliflozin during gestation and lactation (at ~1500 times the clinical exposure), as well as in juvenile rats treated directly with dapagliflozin (NOEL not established).
- Dapagliflozin-treated juvenile rats were more prone to hypoglycaemia and metabolic acidosis than adults and had delayed growth. The findings in juvenile animal studies raise concerns for any future paediatric indication.

Limitations:

- The metabolite dapagliflozin 3-O-glucuronide was less prominent in the non-human species studies than in humans.
- The urinary route of excretion was dominant in humans but not in dogs whereas the faecal and urinary routes were both used by rodents.
- No nonclinical studies on pharmacokinetic or toxicological interactions with the proposed combination therapies were included in the submitted data.
- Some variability in dapagliflozin exposure may be seen in patients containing one of a number of naturally-occurring polymorphisms of the UGT1A9 gene (or flanking region) which affects the activity or expression level of this enzyme.
- Repeat dose toxicity studies did not use a primate species (cynomolgus monkeys) although one was used in the pharmacokinetic studies.

The evaluator recommended some presentational and content changes to numerous sections of the draft product information document (PI).

Clinical

The evaluator notes that the clinical data package included reports on 26 completed studies of the pharmacokinetics and pharmacodynamics of dapagliflozin, as well as another which was not proceeded with, and 14 reports of Phase IIb and Phase III clinical studies, some of which have ongoing extensions.

The film-coated tablets that are proposed for marketing are similar to those used in the Phase III studies, with minor modifications of colorant in the film coat, tablet shape, embossing and the technical grade of the microcrystalline cellulose excipient.

Pharmacokinetics and pharmacodynamics:

The evaluator could identify 632 subjects (including 118 Type 2 diabetics) that were exposed to dapagliflozin in 26 studies, at some minor variance from the sponsor's total of 635. As listed by the evaluator, the Phase I and II data package included:

- eight single and multiple dose studies, in which single oral doses from 2.5 to 500 mg and multiple oral doses from 2.5 to 100 mg of dapagliflozin for up to 14 days were evaluated in healthy subjects.
- multiple oral doses from 5 to 100 mg of dapagliflozin for up to 14 days were evaluated in subjects with T2DM.
- ten drug-drug interaction studies in healthy subjects evaluating dapagliflozin in combination with other oral anti-diabetic medications, commonly co prescribed cardiovascular medications and with rifampicin which is an inducer of several drug metabolising enzymes.

Pharmacokinetic data were consistent with the other evaluators' findings:

- Following oral ingestion and independently of dose, dapagliflozin is absorbed rapidly and appears in the circulation with a T_{max} of approximately 1 h.
- Dapagliflozin has a high volume of distribution; 118 L.
- Dapagliflozin is transported in plasma in protein bound form, protein binding is estimated at 90-96% so accounting for part of the volume of distribution.
- Conversion to the inactive metabolite dapagliflozin 3-O-glucuronide under the influence of UGT 1A9 occurs in both liver and kidney and is the major clearance pathway for dapagliflozin. There is only one active but minor metabolite; BMS-511926.

- The major route of elimination for dapagliflozin is urinary excretion; following administration of ^{14}C-labelled dapagliflozin in mass balance Study MB 102006, 75% of the radioactivity was recovered in the urine, mostly in the first 24 h and in the form of metabolites, principally dapagliflozin 3-O-glucuronide. In the same study, most of the remaining radioactivity (21%) appeared in the faeces and of this most (15% of administered dose) was in the form of unaltered dapagliflozin. Renal clearance of dapagliflozin was estimated at 4.3 mL/min (range 3.75 to 5.10).
- At doses of 10 mg and below steady state appeared to have been reached by Day 7.
- There was no evidence of marked inter-individual variability with regard to the pharmacokinetics of dapagliflozin.

Study MB102008 included a pharmacogenetic analysis of 187 subjects who had at least one SNP with dapagliflozin clearance data available. Eight SNPs were identified within the distribution of values for the subjects' dapagliflozin clearance, these genetic variations were estimated by ANCOVA. The conclusion from this study was that variations in the genotype for UGT1A9 are not likely to be responsible for clinically significant effects on the pharmacokinetics of dapagliflozin.

Bioequivalence of the 5 mg and 10 mg tablets that are intended for marketing was not directly shown, "The 5 mg doses given in the studies of dose proportionality … were given using capsules or solution formulations". However, "In all of the PK studies, there is as expected a relationship between dapagliflozin exposure as measured by a variety of AUC parameters and the dose given. This approximates 50 ng.h/mL of AUC per mg of dapagliflozin given and varies very little across the wide dose range (2.5-500 mg) and in the various populations studied." However, body weight of at least 120 kg was associated with somewhat lower systemic exposure at a 10 mg dose than normal or low body weight whereas moderate renal impairment, more predicably, was associated with higher systemic exposure as was age 65 years and older (see CER). Study MB 102007 was an open label, parallel group study in which the effect of varying degrees of renal dysfunction on the pharmacokinetics and pharmacodynamics of dapagliflozin, in patients with Type 2 diabetes was assessed. Progressive renal impairment was associated with higher systemic exposure/reduced clearance as seen in the applicant's tabulation (Table 14).

Table 14. Pharmacokinetic parameters

Diabetic Status, Renal Function Group	Study Day	Dapagliflozin Pharmacokinetic Parameters				
		Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC(TAU) (ng·h/mL) Geom. Mean (CV%)	CLR (mL/min) Geom. Mean (CV%)	%UR (%) Mean (SD)
Diabetic Normal	Day 4 (n=4)	249 (21)	1.00 (0.50, 1.50)	864 (11)	5.22 (38)	1.4 (0.51)
	Day 10 (n=4)	310 (22)	1.00 (0.50, 1.00)	853 (8)	6.51 (34)	1.7 (0.52)
Diabetic Mild	Day 4 (n=4)	410 (23)	1.00 (1.00, 6.00)	1428 (38)	2.37 (54)	1.1 (0.38)
	Day 10 (n=4)	358 (25)	1.00 (1.00, 1.50)	1443 (21)	2.52 (51)	1.2 (0.54)
Diabetic Moderate	Day 4 (n=6)	466 (21)	1.00 (0.50, 1.00)	1807 (31)	2.54 (71)	2.0 (2.15)
	Day 10 (n=5*)	512 (23)	1.00 (0.50, 1.50)	2467 (37)	2.06 (77)	1.8 (1.11)
Diabetic Severe	Day 4 (n=3)	330 (6)	1.00 (0.50, 2.00)	1920 (26)	1.42 (30)	0.9 (0.43)
	Day 10 (n=3)	338 (16)	1.00 (0.50, 1.00)	2207 (27)	1.13 (19)	0.8 (0.31)

Of greater import, efficacy declined, "… with diminishing renal function, a decline in the amount of glycosuria in response to dapagliflozin is seen. With mild, moderate and severe renal impairment, respectively, glucose clearance on Day 1 decreased on average 11.81 mL/min, 20.25 mL/min and 27.00 mL/min by comparison with the normal renal function subjects, and on Day 10 by 14.13 mL/min, 24.22 mL/min and 32.30 mL/min..." See also the discussion of Study MB 102029 in the CER, "...In summary the data, and Study MB 102029 in particular, show that dapagliflozin is relatively ineffective in reducing blood glucose in the presence of moderate renal impairment. The evidence for benefit of using it in the subgroup of patients with eGFR values in the 45-60 mL/min/1.73 m2 range is marginal."

Study MB 102027 (see CER) suggested that exposure to dapagliflozin is progressively increased as liver function deteriorates but it is unclear why the exposure to the principal metabolite rises in parallel.

The population pharmacokinetic analysis suggested no accumulation on repeat dosing, that is, drug exposure remains unchanged at intervals up to 24 weeks of administration.

Dapagliflozin was not shown to interact with metformin, sitagliptin or pioglitazone in studies of 3-period crossover design. With glimepiride, a small increase (12%) in exposure of glimepiride when coadministered with dapagliflozin was not regarded as significant. A study was not done using acarbose or orlistat.

Dapagliflozin did not interact with valsartan or warfarin, raised the AUC of simvastatin by 20% and did interact with a loop diuretic, bumetanide; "Calculating the interaction effect simply using the within group AUC values, however, yields an estimation of the increase in exposure for bumetanide at 28%, and for dapagliflozin 19%, when coadministered…" – see CER for more information including a pharmacodynamic interaction. An interaction was seen with rifampicin but the effect on urinary glucose excretion was modest (circa 10%) (see CER).

Pharmacodynamics, Dose ranging:

The evaluator explains the therapeutic principle of dapagliflozin in these terms:

"The amount of glucuresis, which is glycosuria pharmacologically promoted in this case by dapagliflozin, will be determined by the degree of inhibition of SGLT2 and the quantum of the filtered load of glucose. In turn, it will therefore depend on three factors: the blood glucose level, the glomerular filtration rate, and the effective dose of dapagliflozin."

Three studies contributed information on dose ranging in normal and diabetic patients, "In summary, the minimum effective daily dose of dapagliflozin is 1 mg and the maximum probably 20 mg. The proposed dose of 10 mg gives a near-maximal response of glucuresis at approximately 60 g/24h; as the sponsor points out in their Summary of Clinical Pharmacology, this represents a significant loss of caloric energy approximating 225 kcal (160kJ)." [This conversion is in error – perhaps 945kJ]. For example Study MB 102008, a multicentre, randomised, double blind, placebo controlled parallel group trial to evaluate safety and efficacy of dapagliflozin as monotherapy in drug naïve Type 2 diabetes subjects who were inadequately controlled on lifestyle measures (Table 15).

Table 15. Results from Study MB 102008

Efficacy Measure	BMS 2.5MG N=59	BMS 5MG N=58	BMS 10MG N=47	BMS 20MG N=59	BMS 50MG N=56	PLACEBO N=54	METFORMIN N=56
A1C(%)							
n	57	58	44	57	53	50	54
Baseline Mean (SD)	7.64 (0.70)	8.04 (0.88)	7.95 (0.84)	7.73 (0.94)	7.84 (0.99)	7.85 (0.92)	7.64 (0.77)
Week 12 Mean (SD)	6.99 (0.68)	7.24 (0.94)	7.05 (0.75)	7.21 (0.84)	6.93 (0.83)	7.65 (1.41)	6.97 (0.80)
Adjusted Change from Baseline Mean (SE)	-0.71 (0.09)	-0.72 (0.09)	-0.85 (0.11)	-0.55 (0.09)	-0.90 (0.10)	-0.18 (0.10)	-0.73 (0.10)
Difference from PLACEBO Mean (SE)(a)	-0.53 (0.14)	-0.54 (0.14)	-0.67 (0.15)	-0.37 (0.14)	-0.72 (0.14)		
P-value vs Placebo(*)	0.0001 *	<.0001 *	<.0001 *	0.0073 *	<.0001 *		
P-value for Trend Test	0.4139						

Secondary actions of dapagliflozin include natriuresis, an associated calciuresis and a uricosuric effect. There is also a mild osmotic diuresis. The significance of these actions may be minor but this conclusion by the evaluator is based on limited Phase II studies. There may not be an additive effect with bumetanide but there may be one with hydrochlorothiazide (Study MB 102004, a single dose study see CER).

Interaction studies with penicillins or NSAIDs were not presented.

Clinical efficacy

The 3 Phase IIb studies and 11 Phase III studies shown in the table included 6436 randomized and treated patients with Type 2 diabetes, of whom 4495 were treated with dapagliflozin at doses ranging from 1 mg to 50 mg. The doses used in the Phase III studies were at least one of 2.5 mg, 5 mg or 10 mg per day. The studies were of acceptable design and followed a typical sequence (with slight variations in duration) (see Figure 3 in CER).

The primary efficacy parameter was change in HbA1c, relative to placebo or active control as appropriate, from baseline to the end of the 24 week short term treatment period. The exceptions were Study D1690C000012 (a weight loss study) and Study D1690C00004 (which measured HbA1c at 52 weeks as the primary endpoint). Secondary endpoints included fasting plasma glucose, body weight or BMI and sub analyses of responders.

A specific exclusion criterion, based on the mechanism of action of dapagliflozin, was the presence of severe renal impairment, defined as eGFR <30 mL/min/1.73 m^2.

Rescue medication was given to subjects who failed to meet prespecified glycaemic targets. This varied from study to study but could include metformin, pioglitazone, rosiglitazone, sitagliptin, acarbose, or sulphonylureas.

Monotherapy studies

Drug naïve subjects were recruited, defined as either never having received diabetes medication or having had such for <24 weeks since the diagnosis of diabetes, not for more than 14 days during 12 weeks prior to enrolment and not at all during the 4 weeks prior to enrolment.

Study MB 102013 an international study involving 485 subjects at 85 sites that examined the efficacy of a variety of dapagliflozin regimens in treatment naïve subjects with HbA1c ≥ 7.5 and ≤ 10.0%, having a median duration of diabetes of less than six months. There was a twice-daily tablet regimen, including placebo, with active dapagliflozin treatment being given either in the morning (AM) or evening (PM). Of 1067 enrolled, 513 subjects entered the lead-in period and 485 were randomised to placebo (n=75), dapagliflozin 2.5 mg AM (65), 5 mg AM (64), 10 mg AM (70), 2.5 mg PM (67), 5 mg PM (68) or 10 mg PM (76). A further 74 subjects with more severely uncontrolled diabetes (HbA1c >10.1% but <12.0%), designated as group 2, were randomised to 5 mg dapagliflozin AM or 10 mg AM. As noted by the evaluator, with AM administration, HbA1c fell by 0.23% in the placebo group 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). Body weight fell by 2-3 kg in all groups with a numerically greater reduction of 0.5-1 kg in the dapagliflozin groups, these differences not achieving statistical significance.

There was a long term extension and the results after 99-102 weeks treatment suggested a lessening of benefit despite drop-outs: HbA1c for subjects remaining in the study was lower, by comparison with baseline than at 24 weeks, the mean reduction from baseline was 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 for 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 had discontinued progressively for lack of glycaemic control or for need for rescue therapy.

> *Comment:* this is a modest treatment effect at the recommended dose that is present at 24 weeks but it may not be sustained.

The evaluator found that Study MB 102032 showed similar findings, although the maximal dapagliflozin dose given was 5 mg. This study is described as a Phase III multicentre, international trial of randomised, double blind, placebo controlled, parallel group design. Some 282 diabetic subjects who were inadequately controlled on diet and exercise (141 male; 81% Caucasian; mean age 53, range 18-77; mean weight 85.4 kg, range 43-150) with inadequate control as defined by HbA1c ≥ 7.5 and ≤ 10.0% were randomised into equal sized groups to receive daily doses of 1, 2.5, or 5 mg of dapagliflozin, or placebo.

At 24 weeks, HbA1c in the placebo group was effectively unchanged (rise of 0.02%) and in the 1, 2.5 and 5 mg dapagliflozin groups fell by 0.68%, 0.72% and 0.82% respectively. Body weight fell by 2.64-2.69 kg in the three dosage groups, the result in each being significantly different (p= 0.0018-0.0024) from the placebo group in which the mean weight loss was 0.96 kg.

Study MB 102008 is described as a supportive (Phase IIb) study. It was a 12 week trial, in drug naïve patients, that was placebo controlled and which also had an active control arm using metformin monotherapy. As presented in the application, the results for HbA1c and for the primary efficacy parameter of change from baseline are shown below in Table 16.

Table 16. Results for HbA1c

Efficacy Measure	BMS 2.5MG N=59	BMS 5MG N=58	BMS 10MG N=47	BMS 20MG N=59	BMS 50MG N=56	PLACEBO N=54	METFORMIN N=56
A1C(%)							
n	57	58	44	57	53	50	54
Baseline Mean (SD)	7.64 (0.70)	8.04 (0.88)	7.95 (0.84)	7.73 (0.94)	7.84 (0.99)	7.85 (0.92)	7.64 (0.77)
Week 12 Mean (SD)	6.99 (0.68)	7.24 (0.94)	7.05 (0.75)	7.21 (0.84)	6.93 (0.83)	7.65 (1.41)	6.97 (0.80)
Adjusted Change from Baseline Mean (SE)	-0.71 (0.09)	-0.72 (0.09)	-0.85 (0.11)	-0.55 (0.09)	-0.90 (0.10)	-0.18 (0.10)	-0.73 (0.10)
Difference from PLACEBO Mean (SE)(a)	-0.53 (0.14)	-0.54 (0.14)	-0.67 (0.15)	-0.37 (0.14)	-0.72 (0.14)		
P-value vs Placebo(*)	0.0001 *	<.0001 *	<.0001 *	0.0073 *	<.0001 *		
P-value for Trend Test	0.4139						

Supportive evidence of efficacy was also obtained from inspection of the results of Study MB 102034 (see below).

Overall, the evaluator finds that use in monotherapy is supported at a dose of 10 mg "*with a placebo controlled reduction in HbA1c of 0.6-0.7%, a clinically significant change*".

> *Comment*: this is barely true as far as the pivotal Study MB 102013 is concerned and the benefit beyond 24 weeks is uncertain. It was sensible that Study MB 102008 included a positive control, metformin.

Initial Combination Therapy with Metformin:

Table 17. Study details

Initial combination therapy with metformin		
MB102021 24 weeks	Treatment- naive subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 5 mg + metformin extended release (XR) up to 2000 mg, dapa 5 mg, and metformin XR up to 2000 mg 194-203/397/598
MB102034 24 weeks	Treatment- naive subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 10 mg + metformin XR up to 2000 mg, dapa 10 mg, and metformin XR up to 2000 mg 208-219/430/638

These studies separately tested two doses of dapagliflozin in patients with high initial HbA1c levels. Study MB 102021 enrolled 598 patients and Study 102034 enrolled 638 patients (75% of whom had a duration of diabetes of two years or less) in a 3 armed study in which dapagliflozin in combination with metformin was compared with treatment arms in which the same two medications were given alone to patients who were treatment naïve. In Study 102021, a 5 mg dose of dapagliflozin was used.

In Study MB 102021, drug naïveté was defined as subjects who had either never received oral hypoglycaemic medications or who had received them for <24 weeks since the original diagnosis but not for more than 14 days during the 12 weeks prior to enrolment and not at all for the most recent 4 weeks. Open label rescue medication with pioglitazone 15 mg, sitagliptin, or *acarbose* was permitted in the event of loss of glycaemic control. At 24 weeks, HbA1c had fallen by 1.19% with dapagliflozin 5 mg, 1.35% with metformin and 2.05% with the combination therapy. As stated by the evaluator, "The opportunity to statistically compare the outcomes for dapagliflozin monotherapy with metformin was not taken in this study but it can be seen from the above that at the 5 mg dosage, the outcomes for dapagliflozin are numerically inferior to those for metformin."

In Study MB 102034, the design was similar, in patients who were drug naïve. Patients were randomised to either dapagliflozin 10 mg plus metformin XR up to 2000 mg (211),

dapagliflozin 10 mg (219), or metformin XR up to 2000 mg daily (208). There was no placebo arm, so it is implied that the results do not take account of the probably substantial contribution of diet and lifestyle counselling.

Table 18. Results from Study MB 102034

EFFICACY ENDPOINT STATISTICS	DAPA 10MG + MET (N=211)	DAPA 10MG (N=219)	MET (N=208)
PRIMARY EFFICACY ENDPOINT			
HBA1C (%) AT WEEK 24 (LOCF)			
N#	202	216	203
BASELINE MEAN (SD)	9.10 (1.276)	9.03 (1.272)	9.03 (1.295)
WEEK 24 LOCF MEAN (SD)	7.10 (1.001)	7.59 (1.232)	7.60 (1.420)
MEAN CHANGE FROM BASELINE (SD)	-2.01 (1.079)	-1.44 (1.310)	-1.42 (1.417)
ADJUSTED MEAN CHANGE FROM BASELINE (SE)	-1.98 (0.0759)	-1.45 (0.0734)	-1.44 (0.0757)
95% CI FOR ADJ. MEAN CHANGE FROM BASELINE	(-2.13,-1.83)	(-1.59,-1.31)	(-1.59,-1.29)
COMBINATION GROUP VS. DAPA 10MG			
DIFFERENCE (SE) (a)	-0.53 (0.1056)		
95% CI FOR DIFFERENCE	(-0.74,-0.32)		
P-VALUE (*)	<.0001 *		
COMBINATION GROUP VS. MET			
DIFFERENCE (SE) (a)	-0.54 (0.1072)		
95% CI FOR DIFFERENCE	(-0.75,-0.33)		
P-VALUE (*)	<.0001 *		

Open label rescue medication with pioglitazone 15 mg, sitagliptin, or acarbose was employed in 9 combination, 3 dapagliflozin and 5 metformin subjects.

Statistical comparison of the two monotherapy groups showed dapagliflozin to be non-inferior to metformin with regard to the HbA1c change at 24 weeks and superior (p = 0.0012) in terms of the FPG reduction.

The evaluator regarded the treatment effect obtained from combination therapy to be clinically significant.

Add-on to One Other Drug:Metformin

Table 19. Study details

Add-on combination therapy with metformin		
MB102014 24 plus 78 weeks	Subjects on metformin ≥1500 mg/day with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 135/137/409/546
D1690C00012 24 plus 78 weeks	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥6.5% and ≤8.5%	Dapa 10 mg and placebo 91/91/182

Study MB 102014, a multicentre (n=80), international, randomised, double blind, placebo controlled, parallel group trial, randomised 546 poorly controlled Type 2 diabetes subjects to one of three fixed add-on doses of dapagliflozin or placebo. It is the sole pivotal study in support of this indication. As noted by the evaluator, HbA1c varied between 7.99 and 8.16% in the 4 groups and at 24 weeks it had fallen by 0.30% in the placebo group and by 0.67%, 0.70% and 0.84% in the 2.5, 5 and 10 mg dapagliflozin groups respectively. For the 10 mg dose, fasting plasma glucose was reduced 1.31 mmol/L compared with 0.33 mmol/L for placebo and the majority of this change being evident after one week's treatment.

In the extension phase, drop-outs were few: "Of the 483 subjects completing the short-term period, nearly all (476) entered the 78 week long-term extension. 119 were in the 10 mg dapagliflozin group and of these, 95 (79.8%) completed the study. By comparison, 73/115 (63.5%) of placebo subjects completed the 78 weeks, due to a much higher dropout rate for lack of efficacy (27 compared with 9 subjects). " "In **completing** [Delegate's emphasis] subjects (excluding data after rescue), mean HbA1c in placebo subjects was unchanged (0.02% less) but was reduced from baseline by 0.80% in the 10

mg dapagliflozin group and by 0.50% and 0.6% in the 2.5 and 5 mg dosage groups respectively."

Weight loss was 0.89 kg with placebo and 2.86 kg of dapagliflozin 10 mg. [Of note, this was similar to the week 24 findings of Study D1690C000012, an ongoing weight loss study.]

Study D1690C00004 is described as supportive. However, it was a Phase III international, multicentre (n=95), randomised, parallel group, 52 week double blind study that used an active control. It was conducted in patients who were inadequately controlled on metformin monotherapy.

Table 20. Study details

Active comparator		
D1690C00004 52 plus 156 weeks	Subjects on metformin >1500 mg/day with HbA1c >6.5% and ≤10.0% Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10 mg and glipizide titrated to 5, 10, and 20 mg 406-408/406/814

"At 52 weeks, HbA1c fell by 0.52% in both groups, and noninferiority of the two treatment approaches was clearly shown. Body weight fell by a mean 3.22 kg in the dapagliflozin group compared with a rise of 1.44 kg with glipizide, and the dapagliflozin subjects experienced less hypoglycaemia."

The evaluator concludes, "Together, these studies [Study MB 102014 and Study D1690C00004] provide strong evidence of efficacy of dapagliflozin as add-on therapy for subjects failing with metformin alone, including maintenance of glycaemic response and weight reduction over 1-2 years."

Add-on to Sulphonylurea:

There was one study, D1690C00005, which recruited a population of metformin non-users, many of whom were significantly renally impaired and all of whom were on glimepiride monotherapy.

Table 21. Study details

Add-on combination therapy with SU		
D1690C00005 24 plus 24 weeks	Subjects on SU with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596

The study was a Phase III, international, randomised, 24 week double blind, parallel group, multi-centre, placebo controlled study, with a 24 week extension period, to evaluate the efficacy and safety of dapagliflozin as add-on therapy to glimepiride (a sulphonylurea) in patients with inadequate glycaemic control (HbA1c ≥7% and ≤10.0%). As noted by the evaluator, at Week 24, HbA1c had changed little in the placebo group (-0.15%) and there was a dose related fall (mean and 95% CI, adjusted for the placebo group change), of 0.44% (0.27, 0.61), 0.49% (0.32, 0.67) and 0.68 % (0.51, 0.86) for the 2.5, 5 and 10 mg groups respectively. All groups were significantly different from placebo at $p<0.0001$. FPG was likewise reduced in a dose related fashion by 1-1.5 mmol/L. Body weight fell from baseline by a mean of 0.72 kg in the placebo group and by 1.20, 1.56 and 2.26 kg respectively in the three dapagliflozin groups. HbA1c changes were maintained in the long-term extension period; after 48 weeks the placebo adjusted mean fall from baseline was 0.41%, 0.56% and 0.73% for the 2.5, 5 and 10 mg dapagliflozin groups.

As noted by the evaluator, "There was a significant interaction between HbA1c response at 24 weeks and category of renal function although those with moderate impairment still had a reasonable response (change from baseline, -0.63%)." "For those subjects with normal renal function in the 10 mg dapagliflozin group (47/151), mean change in HbA1c

from baseline to 24 weeks was 0.89%, compared with 0.80% and 0.63% in the mild and moderately impaired (eGFR 60 – 90 and 30 - 59 mL/min/1.73 m2 respectively) groups."

Add-on to Pioglitazone:

Study MB 102030 examined the efficacy of dapagliflozin 5 mg and 10 mg, compared with placebo, when added to pioglitazone 30 mg or 45 mg monotherapy but with poor glycaemic control (HbA1c ≥ 7.0 and ≤ 10.5% on thiazolidinedione alone). It was of multicentre (105 sites in numerous countries), randomised, 24 week double blind, placebo controlled, parallel group design. There were two groups enrolled, making this rather complex:

"There were 2 types of recruitment for this study.

Group 1 consisted of subjects with inadequate control as defined above, taking a stable dose of pioglitazone 30 or 45 mg daily for at least 12 weeks.

Group 2 could be either "drug naïve" defined as no anti-diabetic medication for 10 weeks with HbA1c ≥ 8.0 and ≤ 11.0%; on a stable dose of pioglitazone 15 mg daily or any dose of rosiglitazone for at least 12 weeks, with HbA1c ≥ 8.0 and ≤ 11.0%; or on stable monotherapy with metformin <1700 mg/day or sulphonylurea at half or less of maximal dose for at least eight weeks, with HbA1c ≥ 7.0 and ≤ 10.0%. "

Table 22. Study details

Add-on combination therapy with TZD		
MB102030 24 plus 24 weeks	Subjects on pioglitazone with HbA1c ≥7.0% and ≤10.5%	Dapa 5, and 10 mg and placebo 139-141/281/420

The evaluator commented, "… the majority of subjects (limited to 67% of randomised set by study protocol) had been on a variety of antidiabetic regimens and were switched to pioglitazone for the purpose of the study. It is therefore probable that this study population had an unusually high degree of heterogeneity with respect to previous diabetic medication history and might be variously liable to either respond to or relapse on any new regimen. "

Of 972 enrolled subjects, 420 were randomised, 141 to dapagliflozin 5 mg, 142 dapagliflozin to 10 mg and 139 to placebo. The mean age of the patients enrolled was 53.5 years (range 23-84) and the mean body weight was 86.3 kg (range 47-160). The evaluator noted, "Despite these limitations, a difference from placebo in HbA1c response at 24 weeks was shown, of -0.40% and -0.55% for 5 mg and 10 mg dapagliflozin ($p<0.0001$) respectively. Consistent with the complexities of recruitment, the placebo response itself was clinically significant at -0.42%. "

> *Comment:* Pioglitazone may not work well on its own when used in patients selected in this way.

However, the 48 week data in responders look more favourable, "By 48 weeks, 33.8% of placebo subjects had been discontinued for failing to meet glycaemic targets and requiring rescue therapy, compared with 18.4% of dapagliflozin 5 mg and 11.4% of dapagliflozin 10 mg subjects. Excluding data after rescue, placebo-subtracted mean change from baseline HbA1c was -0.41% for the 5 mg dapagliflozin group and -0.67% for the 10 mg group."

Add-on combination therapy with insulin:

The sole study, Study D1690C00006 was, in the evaluator's words, "… another 'real world' study with a typically obese, insulin resistant and poorly controlled T2DM population with average 13.6 years since diagnosis and six years on insulin therapy. Subjects were taking a variety of other oral agents, as is usual. Median insulin dose was 65 units." It was of randomised, parallel group, 24 week double-blind, placebo controlled design. Inadequate

control **on insulin** was taken as HbA1c ≥7.5% and ≤10.5% therapy. This was a large study: of 1240 enrolled subjects (mean age 59.3 years, range 25-79; 47.0% male, 95% Caucasian; mean BMI 33.4, range 21.9-44.8), 808 were randomised, 202 to 2.5 mg, 211 to 5 mg and 194 to 10 mg dapagliflozin, and 193 to placebo.

"Approximately a third of the subjects had a baseline HbA1c >9%. Median daily insulin dose was 65 units daily with 20% of the subjects on >100 units daily. 50% of subjects were using one or two other oral hypoglycaemic agents, mostly metformin alone (40%), with 5.8% using metformin plus sulphonylurea and a total of 35 subjects (4.4%) using other combinations."

Table 23. Study details

Add-on combination therapy with insulin		
D1690C00006 **24 plus 24 plus 56 weeks**	**Subjects on insulin ≥30 IU/day ± maximum 2 OAD with HbA1c ≥7.5% and ≤10.5%**	**Dapa 2.5, 5, and 10 mg and placebo** **196-212/610/807**

Results are shown in Table 24.

Table 24. Results for Study D1690C00006

	PLA +INS N= 193	DAPA 2.5 MG +INS N= 202	DAPA 5 MG +INS N= 211	DAPA 10 MG +INS N= 194
Primary endpoint				
HbA1c (%) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	-0.30 (0.0521)	-0.75 (0.0507)	-0.82 (0.0493)	-0.90 (0.0515)
p-value vs. PLA +INS		<0.0001 *	<0.0001 *	<0.0001 *
Key secondary endpoints				
Body weight (kg) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	0.02 (0.1833)	-0.98 (0.1786)	-0.98 (0.1734)	-1.67 (0.1814)
p-value vs. PLA +INS		0.0001 *	<0.0001 *	<0.0001 *
Calculated mean daily insulin dose (IU/day) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	5.08 (0.9432)	-1.80 (0.9217)	-0.61 (0.9012)	-1.16 (0.9354)
p-value vs. PLA +INS		<0.0001 *	<0.0001 *	<0.0001 *
Subjects with calculated mean daily insulin dose reduction ≥10% at week 24 (LOCF)				
Percent adjusted	11.0%	18.2%	16.7%	19.6%
p-value vs. PLA +INS		0.0411 *	0.0923	0.0168 *
Fasting plasma glucose (mg/dL) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	3.3 (3.370)	-12.5 (3.247)	-18.8 (3.140)	-21.7 (3.309)
p-value vs. PLA +INS		0.0008 *	<0.0001	<0.0001 *

The evaluator added, "After 48 weeks treatment, at the end of the initial 24 week extension period which was completed by >80% of subjects, outcome data were maintained at very much the same level; for the placebo group, mean HbA1c was down 0.43% from baseline, 0.93% for 10 mg dapagliflozin, and intermediate values for the other doses. " "... dapagliflozin in combination with insulin produced an average additional 0.5% improvement in HbA1c, which was maintained for more than one year, and was effective in preventing upward creep of insulin dosage." A modest insulin sparing effect was shown (see CER).

Clinical safety

The data base for safety is large, "In the 40 included studies, 4922 subjects received at least one dose of dapagliflozin and of these 1373 received 10 mg doses. 1193 subjects

received 10 mg doses for the 24 week short-term phase of the placebo controlled studies and of these, 768 continued with 10 mg daily doses in longer term extensions 24 weeks or longer."

In terms of Phase IIb or Phase III studies, exposure by time for dapagliflozin 2.5 mg or higher was:

- 6months exposure: 3333 subjects
- 12 months exposure: 2232 subjects
- 18 months exposure: 1317 subjects
- 24 months exposure: 441 subjects

Adverse events were reported by slightly higher proportions of 5 mg (61.9%) and 10 mg (61.5%) dapagliflozin subjects by comparison with placebo subjects (56.9%). Some of this increase was related to reporting of hypoglycaemia by 11.4% and 10.7% of the dapagliflozin group subjects respectively, compared with 8.0% by placebo subjects and by an increased incidence of reporting of symptoms suggestive of genital infection (GI) or urinary tract infection (UTI) (Table 7). Hypoglycaemia was more often reported when dapagliflozin was used with insulin or a sulfonylurea; see also mention above of increased levels of glimepiride when given with dapagliflozin. In the insulin study, hypoglycaemic events were reported marginally more commonly (53-60%) in the dapagliflozin groups than with placebo (52%).

GI were most often vulvovaginal candidiasis in females and balanitis in males.

On principle, it would be expected that urinary tract infections and genital infections would be more likely with an agent that causes glycosuria. Other potential events of interest such as fractures and urinary tract stones were not remarkable in these studies. Hypovolaemia was more frequent with dapagliflozin (0.7%) than with placebo or other comparator (0.4%). This is of note given the very commonly reported effects of dapagliflozin on haematocrit (see discussion in CER). There was no excess of cardiovascular events however.

The long term effect of dapagliflozin on renal function is unclear. See discussion in the CER, "In summary, the data suggests that dapagliflozin may cause minor but significant deterioration in renal function particularly in subjects whose renal function is already moderately impaired. These changes are probably reversible although this has not been clearly established."

There was no imbalance of deaths but a slight imbalance of cancer (bladder and later, breast). See the supplementary clinical evaluation report for more detail.

Evaluator's recommendations:

1. Registration of the 10mg tablet is supported for all indications, "as the benefit/risk balance would seem equivalent for all the therapeutic situations involved." However, this is perhaps less qualified than the remarks of the report,

   > "From the submitted evidence, the quantum of benefit is slightly stronger for dapagliflozin given as add-on therapy to metformin, in combination with metformin as initial therapy, or as monotherapy, in drug naïve subjects. A significant proportion of the studies supporting the other indications show HbA1c improvements only just over 0.5% which is arbitrarily regarded as the minimum worthwhile improvement with therapy. To some extent, this may reflect the populations of those studies including a higher proportion of subjects whose diabetes was of longer duration or had already proved resistant to other therapies. Longer term maintenance of improved glycaemic control was not shown, or not tested for, in the studies supporting monotherapy or initial combination therapy,

but was shown for varying intervals between 48 and 102 weeks for all of the add-on indications" and at page 53, "This evaluation would support the suggestion implied at 6.2 that monotherapy be restricted to patients in whom metformin is contraindicated or not tolerated." Moreover, metformin has a long established record of safety.

2. Registration of the 5 mg tablet is not supported because the clinical circumstances which the sponsor suggests as indications for the reduced 5 mg dose should be regarded as situations in which dapagliflozin is contraindicated or at least not recommended. For example, the group of patients specified as being "at risk" is likely to include some with co morbidities including moderate renal dysfunction who are likely to be less responsive to dapagliflozin and accordingly derive less benefit. There may also be applicable restrictions to use of concomitant therapies and, besides, the quantum of clinical data is small. See also comments in the CER.
3. Long-term safety monitoring should continue and should specifically involve vigilance for the development of osteoporosis.
4. Further epidemiological information should be sought regarding the significance attributable to the observation of cases of bladder cancer in the study population, and surveillance for such cases and any further cases of breast cancer, should continue.

Second round clinical evaluation report:

Limited new information was supplied: a report on errata in Study MB 102059, which was evaluated in the first-round clinical evaluation report (CER); and, there is a 50 week report of Study D1690C00012, also evaluated in the first-round CER, which requires comment regarding the issue of bone safety.

Product information changes that were recommended previously and that have been accepted include:

· dapagliflozin not be used in patients with severe renal impairment be extended to those with moderate impairment (eGFR <60 mL/min).

Product information changes that were recommended previously and that have NOT been accepted include:

· dapagliflozin not be used in patients with severe hepatic impairment. In reply, the evaluator considers individual risk:benefit impossible to calculate in the absence of adequate experience [it is the sponsors' own statement that the safety and efficacy of dapagliflozin has not been specifically studied in patients with severe hepatic impairment so impaired glucose production in the liver might have implications for safety] and adds that the current Australian prescribing advice is that glitazones are contraindicated in patients with impaired hepatic function, that metformin should only be used with caution, and that significant precautions are advised with sulphonylureas (such as gliclazide). All of these drugs are listed for co administration with dapagliflozin in the proposed indications. Limitations on these aspects of the indications will severely limit the potential application of dapagliflozin in this patient population.
· a simple recommendation that dapagliflozin not be used in pregnancy has been answered with a statement that dapagliflozin "must not be used during the second and third trimesters of pregnancy". The evaluator points out that this does not rule out use in the first trimester.

In regard to the carcinogenicity concerns, the evaluator has reviewed in detail the case reports of bladder and breast cancer. The numbers of cases are few. The 10 mg dose was associated with proportionately more cases that lower doses. There is so far no evidence of latency between the commencement of study drug and case discovery. No firm conclusion

was made regarding an association with dapagliflozin. Neither chance association nor causality are excluded.

No reply was made by the applicant to the suggestion in the first round CER that there is no case for the 5 mg tablet to be marketed.

Risk management plan

It was noted that the proposed indications are not limited to diabetes mellitus type as far as monotherapy is concerned i.e. dapagliflozin might be used in impaired glucose tolerance.

As noted by the evaluator,

> *"The RMP version 2.1 listed a total of two Important identified risks, eight Important potential risks and seven Important missing information as Ongoing Safety Concerns. It is stated that most of the important identified and potential risks relate to the drug's mechanism of action but liver injury, bladder and breast cancers (all are important potential risks) are unexpected. Routine and additional pharmacovigilance activities and routine risk minimisation activities are proposed in the RMP version 2.1."*

The sponsor's summary of the Ongoing Safety Concerns is acceptable to the evaluator.

An extensive post marketing program of safety studies is planned, including renal, bone, neoplasia and cardiovascular studies. A concern has been raised about this,

> *"there is no assurance provided as to the implementation of the planned post-authorisation pharmaco-epidemiology programmes to monitor these safety concerns if the drug is not approved in either the EU or US. The databases intended to be used for these studies are based in the EU and/or US. The Sponsor has not provided an adequate contingency plan for implementing these studies if the drug is not approved in either the EU or US."*

Specific Australian activities are not planned. Due to some potential for unapproved use to promote weight loss, a health care professional education program may be required as an additional risk minimisation strategy. If this application is approved, the evaluator recommended that the implementation of an RMP, agreed upon by the OPR prior to registration, is imposed as a condition of registration. There is also some concern about the absence of a precaution in the PI about use in heart failure.

Comment: The RMP was to be reviewed by ACSOM.

Risk-benefit analysis

Delegate considerations

Applicant's responses to evaluation reports

A response has been made to the quality report, including updated evidence of compliance with Good Manufacturing Practice.

The response to the nonclinical evaluation report raises no matters of substance.

The response to the clinical evaluation report raises one matter of substance, the statement that Study MB102029 was carried out on renally impaired patients should read "patients with moderate renal impairment".

Delegate's comments

Registration is recommended with respect to chemistry and quality control matters. No direct bioequivalence study was undertaken to relate the 5 mg and 10 mg tablets.

The developmental program broadly satisfies the adopted Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus except in regard to item 4 (efficacy endpoints pertaining to the complications of diabetes mellitus).

An antidiabetic agent or an agent acting independently of a glucose-lowering effect may seek to slow the progression of diabetic complications.

Overall a clearly documented and clinically significant change in the natural history of a diabetic complication would be considered as a primary measure of efficacy. Unfortunatley valid intermedicate markers of most of the long term complications of diabetes which could be used in clinical trials are currently lacking. Before undertaking such studies, sponsors are invited to seek scientific advice from the CPMP. In designing such trials, the means for patients to achieve adequate glycaemic and blood pressure control will have to be provided.

Hard endpoints are still required for claims relating to macrovascular disease. (i.e. morbidity/morality trials).

For retinopathy, endpoints based on the progression of diabetic retinopathy documented on well validated grading scales, are considered clinically meaningful. Dilated ETDRS (Early Treatment Diabetic Retinopathy Study) standard seven-standard field stereoscopic 30° fundus photography obtained by a skilled photographer, and compared to standard photographs by a skilled reader, are currenty the ony well validated way to document the effect of treatment on a non proliferative diabetic retinopathy. Progression my be defined as a change from baseline of 2 steps in patients without pre-existing retinopathy (3 steps in patients with pre-existing retinopathy) on the ETDRS scale. The ETDRS severity scale is unsuitable to evaluate diabetic macular oedema. Progression of macular oedema to the centre of the fovea, i.e. to immienently sight-threatening macular oedema is a clinically meaningful outcome; the definition of progression shuld be justified by the applicant. Recent technologies may provide a means to standardise the photographs and document other aspects (e.g. leakage) of diabetic retinopathy. The images they provide still have to be demonstrated acceptable surrogate endpoints.

For nephropathy, hard endpoints are time for doubling of baseline serum creatinine, or sustained increase in serum creatinine, e.g. to greater than 250 µmmol/L, and the evolution to end-stage renal failure defined as need for aintenance dialysis or transplantation. Regarding intermediate endpoints, delay of progression to macroalbuminuria is a relevant measure, particularly if supported by long-term data (of at least 24 months) indicating a favourable evolution of glomerular filtration rate. Delaying the progression to diabetic nephropathy in clinically relevant manner over and above that explained by effects on blood pressure and/or glycaemic control would be sufficient for a specific claim.

Diabetic neuropathy is not a single entity but a number of different syndromes, and no gold standard exists for its assessment. There are markers of progression, but the extent of specific improvement to provide evidence of clinically relevant benefit has not been fully evaluated. The evaluation of efficacy should be based on clinical signs and symptoms. Efficacy variables based upon electrodiagnostic tests (assessing nerve conduction velocity or amplitudes), quantitative sensory tests (for vibration, tactile, thermal warming and cooling thresholds), and quantitative autonomic function tests (assessing heart rate variation with deep breathing, valsalva manoeuvre and postural testing) may be supportive.

The indication regarding Monotherapy is not appropriate. First, it does not refer to Type 2 diabetes.

The indication relating to combination therapy is not precise enough: "insulin (alone or with up to two oral anti-diabetic medications)" is an example of "future-proofing".

The clinical evaluator remarked, "A potential benefit of this approach [the selective inhibition of renal tubular sodium-glucose co transporter Type 2] may be freedom from some of the disadvantages of those diabetes therapies which increase the secretion or enhance the action of insulin, such as hypoglycaemia and weight gain." Equally, one could equally say a priori that dapagliflozin might exacerbate the hypherpahgia and gluconeogenesis of diabetes mellitus and increase the risk of volume depletion, UTIs, GIs, stones or lean muscle mass wasting, for example. That is, it would simply shift the approach from affecting insulin resistance or adding extra insulin towards making it harder to sustain hyperglycaemia. However, not all of these particular safety signals have emerged so far.

The efficacy of dapagliflozin in monotherapy is modest but it has consistently been shown to have additive effects in glycaemic control in combination with one each of several classes of oral antidiabetic drugs. An exception is pioglitazone; the study was elaborate in design but likely failed to show worthwhile benefit for reasons implied by the evaluator.

Dapagliflozin offers the advantage of modest weight loss and would seem to have potential for use with other agents that are neutral in respect of weight gain or that are also associated with modest weight loss. Dapagliflozin would therefore seem to be placed against DPP-4 inhibitors in this role but no comparative data are available. The specific weight loss study, D1690C000012, has not yet finished its long term extension phase. However, the benefits so far are modest, "The fact that 30% of subjects lost at least 5% of body weight against an overall average loss of 2 kg shows that the response is highly variable." The modest short term weight loss may be somewhat based upon increased sodium and water excretion.

Combined use with DPP-4 inhibitors has not been specifically explored in this data package, a matter that will disappoint prescribers. The use of dapagliflozin with GLP-1 analogues has not been studied but additive effects on weight loss might be of potential concern since a minority of patients receiving GLP-1 analogues experience significant weight loss. Therefore, the PI should caution against such use until clinical trial data are available.

Combination with pioglitazone would seem to be less useful from the point of view of weight control; in the one study presented, the evaluator reported, "These placebo subjects gained an average 1.64 kg, possibly reflecting the recent introduction of pioglitazone. With combination pioglitazone/10 mg dapagliflozin, a mean loss of weight of 0.14 kg was found." It is difficult to interpret this small difference at 24 weeks, given that pioglitazone acts to retain sodium and water and that dapagliflozin will antagonise this action. Perhaps that is the basis for the small difference. It is less clear that there has been an impact on the deposition of fat in this largely pioglitazone naïve population. Another safety concern with thiazolidinediones would be additive effects on bony structure and an increased medium term risk of fracture. More clinical data are needed to address this particular added risk for this drug class.

In the absence of nonclinical data regarding dapagliflozin in combination with other anti-diabetic agents, the safety of the proposed combinations will need to be addressed by clinical data alone.

The first of these other agents that merits consideration is pioglitazone. Pioglitazone has an unresolved issue regarding bladder cancer that also has some nonclinical correlation so it would seem to be very unwise to allow combined use with dapagliflozin until concerns

regarding bladder cancer have been resolved for both drugs. The sponsor might wish to undertake some combination toxicology studies, including in rats and a primate species. Regarding efficacy, given the unlikely recruitment in the pivotal Phase III study resulting in heterogeneity of the population and the lack of a majority of patients who were truly failing pioglitazone monotherapy, it would prudent not to approve the use of dapagliflozin with pioglitazone at present.

There are no nonclinical data on combinations with metformin but tolerability of the combination has so far been acceptable. Nonetheless, volume depletion and exacerbation of renal impairment are possible toxicities. Therefore, use with metformin can only be entertained in persons who are at low risk: those with normal renal function, aged under 65 years, who are normotensives and who have no history of bladder cancer.

Because dapagliflozin works best in those with normal or close to normal renal function, it would seem to be notionally less useful in the very elderly and in those with moderate to severe renal impairment and it should not be used the latter population. If the response to treatment with dapagliflozin deteriorates, this would imply increasing renal impairment. Dapagliflozin should not be used in patients on loop diuretics.

Use with insulin is problematical in this application. Ideally, several studies should could been conducted, for example use with a long acting basal insulin (in which the outcomes of insulin sparing effect, smaller postprandial glucose excursion and weight control would have been of interest), use with a basal:bolus regimen and use with basal insulin +/- GLP-1 agonist (in which an interaction between nausea and vomiting and the risk of dehydration would be a safety outcome of interest). The one Phase III study that has been submitted arguably addresses most of the points in the guideline on one pivotal study <http://www.tga.gov.au/pdf/euguide/ewp233099en.pdf> but dapagliflozin employs a "new pharmacological principle". However, pioglitazone is only approved in dual therapy with insulin so cannot be included in an indication involving insulin and dapagliflozin. The study did not use DPP-4 inhibitors.

There are reservations about long term safety but there are small numbers in respect of serious adverse events (for example, hepatic, cancer). In respect to cardiovascular events, the picture changes with experience in higher risk patients (Studies 18 and 19). The following tabulation is from the applicant's response to a TGA request for information (Table 25).

Table 25.

Summary of results for primary composite endpoint and MACE endpoint in CV analyses of the dapagliflozin Phase 2b/3 clinical programme

	Number of events	HR	95% CI	98% CI
CV meta-analysis for NDA – July 2010 database				
Primary endpoint[a]	78	0.674	0.421, 1.078	0.385, 1.178
MACE[b]	64	0.596	0.357, 0.996	
Supplemental CV meta-analyses (includes -018/-019) – 15 July 2011 database				
Primary endpoint[a]	145	0.819	0.583, 1.152	
MACE[b]	111	0.793	0.537, 1.170	
Analyses in patients with a history of CV events (all studies including -018/-019)				
Primary endpoint[a]	100	0.872	0.577, 1.318	
MACE[b]	75	0.861	0.534, 1.388	
Studies -018 and -019				
Primary endpoint[a]	60	1.068	0.643, 1.772	
MACE[b]	43	1.266	0.693, 2.311	

[a] Time to first event of adjudicated CV death, MI, stroke and hospitalisation for unstable angina.
[b] Composite endpoint of CV death, MI and stroke.

These reservations arise from the experience of more than a decade in respect of the use of intermediate endpoints in endocrine therapy: that markers of glycaemia in diabetes mellitus or weight loss with anorectic agents are not always predictive of overall clinical benefit or able to exclude significant harm. Examples include rimonabant, muraglitazar and Exubera.

The *Add-on Combination* indication is of some concern because most of the patients can be expected to have co morbidities, obvious or not, and one benefit of dapagliflozin (weight loss) is less likely to be maintained in the presence of treatment with insulin or insulin secretagogues (or pioglitazone). Moreover, the nonclinical data do not provide support for multiple drug therapies.

Finally, the risk management activities and pharmacovigilance program depend upon marketing in at least one of the USA or the EU. This is unlikely to occur in the short term.

Therefore, the Delegate was inclined to think that dapagliflozin might best be used as second-line monotherapy, first line combined therapy with metformin in patients with poor prospects for response to metformin monotherapy and in dual combination therapy with metformin or a sulfonylurea. The use of dapagliflozin with insulin seems marginal owing to underlying safety issues including higher background absolute risk of cardiovascular adverse events and higher risk of UIT and GI with dapagliflozin. Perhaps

the extension study or Studies 18 and 19 will provide greater perspective on longer tem safety.

If approved, the Indications could be:

Initial combination

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with Type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy. [Rationale: the combination works in patients with high HbA1c levels and is unnecessary otherwise]*

Monotherapy

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated as an adjunct to diet and exercise in patients with Type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated. [Rationale: not for use in IGT; metformin is not usable in severe renal impairment and dapagliflozin is not as effective in moderate and severe renal impairment].*

Add-on combination

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated in patients with Type 2 diabetes mellitus to improve glycemic control in dual or triple combination with one or both of metformin, a thiazolidinedione (TZD), a sulfonylurea (SU), or insulin alone-when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. [Rationale: use with any thiazolidinedione is not supported; use with GLP-1 analogues was not studied and DPP-4 inhibitors were not formally evaluated.]*

The Committee's advice was sought on these matters and any others that it feels to be relevant.

Conditions of registration

If registered, supply should be conditional upon delivery of the proposed risk management plan.

References to weight loss in the PI should mention that this has so far been shown in regard to secondary endpoints, the specific weight loss study not having been completed. Moreover, morbidity and mortality benefits have not been shown. The adopted guideline states, "Large clinical trials should be performed in patients with well-defined obesity to demonstrate efficacy and safety with long-term use." and "In view of the goals of treatment of obesity, drugs used to treat it should be shown to have no deleterious effects on cardiovascular risk factors."

Proposed actions

The application by Bristol-Myers Squibb Australia Pty Ltd to register dapagliflozin, presented as film coated 5 mg and 10 mg tablets for the proposed indications:

"Monotherapy

> Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated as an adjunct to diet and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance.

Initial combination

> Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve

glycemic control in patients with Type 2 diabetes mellitus when dual dapagliflozin and metformin therapy is appropriate.

Add-on combination

> Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated in patients with Type 2 diabetes mellitus to improve glycemic control in combination with metformin, a thiazolidinedione (TZD), a sulfonylurea (SU), or insulin (alone or with up to two oral anti-diabetic medications) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control."

should not be approved because the data do not support these indications for numerous reasons. The Committee expressed concern at the limitations of the nonclinical data set. Dapagliflozin may be registered for these indications:

Initial combination

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with Type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy.*

Monotherapy

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated as an adjunct to diet and exercise in patients with Type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.*

Add-on combination

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated in patients with Type 2 diabetes mellitus to improve glycemic control in dual or triple combination with one or both of metformin or a sulfonylurea (SU) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.*

subject to provision of agreed risk management initiatives. If these cannot proceed, registration should not proceed or be relinquished.

The Committee's advice was sought.

Response from sponsor

Summary of the Delegate's recommendations and the sponsor's proposed actions

The Delegate stated that dapagliflozin may be registered for modified Initial Combination, Monotherapy and Add-on Combination indications subject to provision of agreed risk management initiatives. The proposed Risk Management Plan (RMP) initiatives were discussed at the Advisory Committee on Safety of Medicines (ACSOM) meeting held on 24 February 2012. The TGA agreed to provide the sponsor with the ACSOM recommendations as soon as these are ratified in order to allow the sponsor to submit a separate response for consideration at the ACPM meeting.

The sponsor welcomes this proposal and proposes the following; to:

- retain the use with insulin indication based on data
- withdraw the indication for Add-on combination use with thiazolidinediones (TZDs)
- withdraw the dapagliflozin 5 mg presentation
- submit a separate response to the ASCOM recommendations for RMP

- Additionally, the sponsor has comments on a number of issues raised by the Delegate and these are presented below.

Proposed indications

Issue 1: The Delegate has proposed modification to the requested indications.

Response: The sponsor's proposed actions regarding the Delegate's recommendations are outlined below. See Indications in the proposed PI for full text of the proposed revised indications:

Monotherapy: The sponsor agreed with the Delegate's recommendation.

Initial Combination: The sponsor agreed with the Delegate's recommendation.

Add-on Combination: The Delegate proposed modification as follows to avoid "future proofing": Forxiga is indicated in patients with Type 2 diabetes mellitus to improve glycemic control in dual or triple combination with one or both of metformin or a sulfonylurea (SU) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

The sponsor agreed that the recommended modification is appropriate regarding the removal of use in combination with TZDs but does not agree that the data warrant a specific indication for triple oral therapy unless with insulin as supported by the Add-on to insulin study. The following modification of the Add-on combination indication is proposed: Forxiga is indicated in patients with Type 2 diabetes mellitus to improve glycemic control:

In combination with metformin, when metformin alone with diet and exercise does not provide adequate glycemic control;

- *in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycemic control;*
- *in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.*

Issue 2: The Delegate commented on use with insulin. The Delegate's proposed indication for Add-on Combination excludes insulin. In addition, regarding the Add-on Combination indication, the Delegate commented that *"The Add-on Combination indication is of some concern because most of the patients can be expected to have co morbidities, obvious or not, and one benefit of dapagliflozin -weight loss -is less likely to be maintained in the presence of treatment with insulin or insulin secretagogues (or pioglitazone)."*

Response: It is the sponsor's position that the clinical data support the inclusion of insulin in the Add-on Combination indication and thus it is retained in the proposed indication. Available data pertaining to Add-on Combination use with insulin or pioglitazone do not support the Delegate's assertion that weight loss is unlikely to be maintained in the presence of these agents. The relevant data regarding add-on use with insulin are summarised below:

As pointed out by the clinical evaluator and the Delegate, Study D1690C00006 (Study 06) is a large study conducted in a 'real world' setting. It included a challenging patient population with long lasting diabetes, who were typically obese with poor glycemic control despite receiving treatment with insulin. Half of the subjects received insulin only as background medication whereas the other half received up to 2 oral antidiabetic drugs in addition. Subjects who received only long acting insulin as well as those receiving a basal: bolus regimen were included. Dapagliflozin was effective in all of these subgroups in improving HbA1C control, body weight loss and insulin-sparing.

The benefit of dapagliflozin taken against a background of insulin is best illustrated by comparing effects of placebo versus dapagliflozin when excluding or including data after insulin up-titration (see Table 26). Excluding data after insulin up-titration, placebo subjects showed HbA1c reduction of -0.43% after 48 weeks. However, 41.5% of placebo subjects received significant insulin up-titration over this period (defined as up-titration of at least 5 IU and 10% above baseline), with a calculated mean increase in daily dose of insulin of 10.53 IU. When including data after insulin up-titration, HbA1c reduction was still just -0.47% after 48 weeks. Importantly, when excluding data after insulin up-titration, placebo subjects showed stable weight, with a -0.17 kg decrease after 48 weeks. When including data after insulin up-titration, placebo subjects showed an increase in body weight of +0.85 kg after 48 weeks. Thus, increased insulin dose was not associated with an improvement in glycemic control and was associated with weight gain in the placebo subjects.

In contrast to results in the placebo group, daily insulin dose in subjects receiving dapagliflozin 10 mg remained almost unchanged after 48 weeks (mean reduction -0.70 IU, see Table 26). Excluding data after insulin up-titration, HbA1c was reduced by -0.92% after 48 weeks and body weight was reduced by -1.79 kg within this time. Including data after insulin up-titration, a body weight loss of -1.45 kg was still observed (keeping in mind that only 15.5% of dapagliflozin subjects had insulin up-titration).

Thus, the use of dapagliflozin added on to insulin was associated with an insulin-sparing effect, with improved glycemic control and with body weight loss rather than gain. This effect has now been substantiated with long term results.

After completion of the planned 2 years of treatment in Study 06, the calculated mean insulin dose in the placebo arm further increased by 18.34 IU, which was associated with a weight increase of 1.79 kg. The dapagliflozin 10 mg arm maintained a stable insulin dose over this period (total change of -0.83 IU) and recent data not yet provided to TGA (and summarised in Table 26) show that HbA1c reduction and weight loss were also maintained for 2 years with dapagliflozin treatment.

In summary, within a challenging patient population, dapagliflozin treatment added on to a background of insulin treatment produced benefits with regard to HbA1c and weight reduction and allowed patients to avoid significant increases in insulin dose. These benefits were maintained for up to 2 years.

Table 26.

Summary of effects of dapagliflozin as add-on therapy to insulin on insulin dose, HbA1c and body weight at Weeks 48 and 104 (Study 06)

Time point Excl or incl data after insulin up-titration	n (%) discontinued or received insulin up-titration[a]		Calculated mean insulin dose (IU/d) adj change from baseline (SE)		HbA1c (%) adj mean change from baseline (SE)		Body weight (kg) adj mean change from baseline (SE)	
	Pla N=193	Dapa 10 mg N=194	Pla N=193	Dapa 10 mg N=194	Pla N=193	Dapa 10 mg N=194	Pla N=193	Dapa 10 mg N=194
Week 48	80 (41.5)	30 (15.5)						
Excluding	NA	NA	NA	NA	N=89 -0.43 (0.0689)	N=139 -0.92 (0.0582)	N=89 -0.17 (0.3018)	N=141 -1.79 (0.2558)
Including	NA	NA	N=157 +10.53 (1.4853)	N=166 -0.70 (1.4432)	N=157 -0.47 (0.0587)	N=164 -1.01 (0.0577)	N=157 +0.85 (0.2717)	N=166 -1.45 (0.2654)
Week 104	95 (49.2)	50 (25.8)						
Excluding	NA	NA	NA	NA	N=50 -0.06 (0.0986)	N=100 -0.71 (0.0753)	N=50 +0.91 (0.4884)	N=102 -1.97 (0.3645)
Including	NA	NA	N=104 +18.34 (2.3424)	N=140 -0.83 (2.1799)	N=107 -0.43 (0.0757)	N=139 -0.79 (0.0698)	N=107 +1.79 (0.3929)	N=141 -1.40 (0.3622)

[a] Discontinued refers to discontinuations due to lack of glycemic control

Source: Week 104 CSR for Study D1690C00006.

adj Adjusted; Dapa Dapagliflozin; NA Not applicable; Pla Placebo; SE Standard error.

Issue 3: The Delegate recommended against the use of pioglitazone with dapagliflozin.

Response: The sponsor agreed to withdraw pioglitazone (TZDs) from the proposed indication for Add-on Combination (see Issue 1 and Indications in the proposed PI) and has removed Study MB102030 data from the *Clinical Trials section*. Text relating to interactions with pioglitazone has been maintained in the proposed PI. However, the sponsor points out that available data have not identified any risk associated with combination use with dapagliflozin and pioglitazone.

Risk management plan issues

Issue 4: In relation to the RMP the Delegate stated that "Finally, the risk management activities and pharmacovigilance program depend upon marketing in at least one of the USA or the EU-this is unlikely to occur in the short term."

Response: The sponsor understands that an RMP acceptable to the TGA is required before approval and registration can occur. CHMP[58] opinion is expected on 19 April 2012. A separate response to the ASCOM recommendations for RMP will be submitted for ACPM consideration.

The sponsor also advised that a number of changes to the RMP have been made in version 3.2 compared to the version most recently evaluated by the TGA (version 2.1). The changes include an updated summary of plans for the cardiovascular (CV) Outcome Study, updated analyses on key safety issues such as bladder and breast cancer and addition of a Drug Utilization Study (DUS). The DUS will be conducted in EU and will specifically describe (1) initiation of dapagliflozin in elderly patients (75 years and older), (2) combination use with loop diuretics and pioglitazone, (3) use in patients with a known history of severe renal impairment, defined as end stage renal disease or dialysis, and (4) use in patients without a diagnosis code for Type 2 diabetes.

[58] CHMP =t he Committee for Medicinal Products for Human Use, formerly known as Committee for Proprietary Medicinal Products (CPMP).

Other PI amendments

Issue 5: Regarding use with metformin the Delegate commented that *"Nonetheless, volume depletion and exacerbation of renal impairment are possible toxicities. Therefore, use with metformin can only be entertained in persons who are at low risk: those with normal renal function, aged under 65 years, who are normotensives and who have no history of bladder cancer."*

Regarding the use of dapagliflozin more generally, the Delegate stated that *"Because dapagliflozin works best in those with normal or close to normal renal function, it would seem to be notionally less useful in the very elderly and in those with moderate to severe renal impairment and it should not be used the latter population. If the response to treatment with dapagliflozin deteriorates, this would imply increasing renal impairment. Dapagliflozin should not be used in patients on loop diuretics."*

Response: The sponsor believes that through the restrictions for dapagliflozin use with regard to renal impairment, elderly patients, patients taking loop diuretics and patients at risk for volume depletion, outlined in the proposed PI, combined with those delineated within the Australian metformin PI, dapagliflozin is efficacious and safe for treatment of Type 2 diabetes in combination with metformin as well as overall. To ensure appropriate and safe use of dapagliflozin, the sponsor proposes to strengthen the language as described below:

Renal impairment: Dapagliflozin is not associated with a deleterious effect on renal function. SAEs of renal impairment are balanced across treatment groups, and there are no cases of acute tubular necrosis, acute nephritis, or end-stage renal disease in the dapagliflozin program. Renal effects that are observed with dapagliflozin are transient, reversible changes in laboratory parameters, consistent with a mild diuretic effect, and can be attributed to reversible hemodynamic changes.

The sponsor acknowledged that a decline in efficacy of dapagliflozin could indicate a decline in renal function into the moderate renal impairment range (defined as CrCl <60 ml/min or eGFR <60 L/min/1.73 m^2). However, it should be kept in mind that a decrease in efficacy could be caused also by other factors, such as a change in medication compliance. The sponsor proposed to include text in the PI to provide this guidance with regard to renally impaired patients (see *Precautions* in the proposed PI):

The efficacy of Forxiga is dependent on renal function. Forxiga should not be used in patients with moderate renal impairment (eGFR <60 mL/min/1.73 m2 by MDRD or CrCl <60 mL/min by Cockcroft-Gault). Therefore, as in all diabetic patients, renal function should be monitored prior to initiation of FORXIGA and periodically thereafter. (see Dosage and Administration, Precautions and Adverse Effects).

Elderly (≥65 years): It is the position of the sponsor that the proposed PI restrictions related to renal impairment, risk for volume depletion and use of loop diuretics maintain a positive benefit:risk profile for dapagliflozin in the elderly aged 65 years or older.

However, due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended for these patients (see *Precautions* in the proposed PI).

Diuretic-related effects: The diuretic-related effects of dapagliflozin are mild and do not lead to long-term sequelae in the target population or in restricted populations. Serious adverse events of volume depletion, including hypotension, are rare and balanced between dapagliflozin and placebo groups. Where imbalances in diuretic-related events occur, they are non-serious, transient events, consistent with the action of a modest diuretic agent. Clinicians are familiar with prescribing diuretics and diuretic combinations in patients with T2DM, and with identifying clinically relevant volume depletion in such patients. The proposed PI clearly identifies dapagliflozin as a diuretic agent, provides

recommendations on the avoidance of volume depletion, and excludes the most susceptible populations from therapy (see Precautions). The proposed PI has been modified to exclude the use of dapagliflozin in patients taking loop diuretics or those that are volume depleted (see Precautions). The Sponsor interprets the Delegate's comment about 'normotensives' as relating to patients with hypotension, addressed here and in the proposed PI, and not to patients with hypertension. There is no evidence to suggest that there is any risk associated with dapagliflozin use in patients with hypertension; in fact, available evidence suggests that there may be a blood pressure-lowering effect of dapagliflozin in these patients.

History of bladder cancer: The sponsor does not propose specific restrictions in the PI with regard to patients with a history of bladder cancer. The sponsor referred to the RMP for a full discussion of the proposed pharmacovigilance activities with regard to events of bladder cancer.

Issue 6: Regarding possible combined use with GLP-1 and DPP-4 analogues, the Delegate requested that *"...the PI should caution against such use until clinical trial data are available."*

Response: The sponsor acknowledged that dapagliflozin has not been studied in combination with GLP-1 and DPP-4 analogues but also notes potential effects of these combinations would need to be explored further to determine if additive effects on weight or other variables are beneficial. A statement that these combinations have not been studied has been added to *Precautions* ('Combinations not studied') in the proposed PI.

Issue 7: The clinical evaluator recommended against use in patients with severe hepatic impairment and questioned the benefit:risk balance for the 5 mg dose. The Delegate did not specifically comment on these points.

Response: The sponsor has modified the PI to recommend that dapagliflozin is not used in patients with severe hepatic impairment (see *Pharmacokinetics* and *Dosage and Administration* in the proposed PI). As the proposed PI has been modified to also exclude use in patients taking loop diuretics or those volume depleted (see *Precautions*), as well as to include precautionary language for patients at risk for volume depletion, the sponsor has deleted the 5 mg presentation from the proposed PI.

Correction/clarification of statements in DRA

Issue 8: Regarding cardiovascular events associated with dapagliflozin, the Delegate commented that *"In respect of cardiovascular events, the picture changes with experience in higher risk patients (studies 18/19)."*

Response: The original CV meta-analysis conducted in 2010 to support the Category 1 application, demonstrated no CV harm with dapagliflozin treatment. The results from the 15 July 2011 supplemental CV meta-analysis are consistent with the original meta-analysis, including patients at high CV risk (from across the program, including from Studies 18 and 19). While the relative risk point estimates for the overall meta-analysis and Studies 18/19 numerically differ, the estimate from Studies 18/19 is based upon a small difference in few events, which is not surprising given these trials were not designed, powered or intended to be examined in isolation. When the uncertainty around point estimates is taken into account, confidence intervals are found to be wide and overlapping, resulting in no evidence of heterogeneity between the results of trials in the overall meta-analysis, including 18 and 19. The p values for the heterogeneity of results between trials in the meta-analysis (p=0.29 for primary, p=0.65 for MACE) do not suggest any true inconsistency in outcomes across studies.

Issue 9: Regarding the advantage of weight loss associated with dapagliflozin, the Delegate commented that "The specific weight loss study, D1690C000012, has not yet finished its long term extension phase. However, the benefits so far are modest, "The fact that 30% of

subjects lost at least 5% of body weight against an overall average loss of 2 kg shows that the response is highly variable." The modest short term weight loss may be somewhat based upon increased sodium and water excretion." Also in relation to weight loss, the Delegate stated that "References to weight loss in the PI should mention that this has so far been shown in regard to secondary endpoints….".

Response: The sponsor clarified that the weight loss associated with dapagliflozin has been shown to be primarily due to fat loss and not due to increased sodium and/or water excretion. The data that support this conclusion are reviewed below:

Change in body weight was a key secondary objective in the majority of Phase III studies and text stating this has been added to the proposed PI, as suggested by the Delegate (*Clinical Trials* section). A modest mean reduction in total body weight relative to placebo or comparator was seen. Differences versus placebo at 24 weeks in the 5 placebo controlled Phase III trials that evaluated dapagliflozin 10 mg and weight loss as a secondary endpoint were; -0.97 and -0.87 (AM and PM dosing, respectively), -1.97, -1.54, -1.78 and -1.68 kg, respectively (see the sponsor's *Summary of Clinical Efficacy* [SCE]). In general, there was a small, rapid reduction in mean weight during the first week followed by a gradual reduction for the duration of the 24 weeks, reaching a plateau at 24 weeks and remaining relatively stable through Week 52 or Week 102 (see SCE). In the designated body weight and body composition study (D1690C00012 [Study 12]) with 2 treatment arms (dapagliflozin 10 mg or placebo added on to metformin), body composition was evaluated using whole body dual-energy X-ray absorptiometry (DXA) (Study 12 24w CSR); these data were provided to the TGA in the sponsor's response of 26 October 2011. Weight loss was the primary endpoint in this study. The placebo corrected weight loss was -2.08 kg at 24 weeks. In the dapagliflozin group, the adjusted mean weight loss was -2.96 kg; the main part of the weight loss was fat mass (-2.22 kg) and a minor part was lean tissue mass (-1.1 kg) as can be expected with weight reduction due to caloric loss.[59] Due to the relatively greater amount of fat loss, the percentage lean tissue mass actually increased in the dapagliflozin group (+1.2%), whereas there was no change in the placebo group after 24 weeks of treatment (Study 12 24w CSR). The variability in weight loss between individual subjects was low, with the majority of subjects (52.8%) in the dapagliflozin group having a 3% weight loss, 30.5% a 5% weight loss and only 1 subject out of 89, a 10% weight loss. Preliminary data up to 2 years in Study 12 show that the placebo corrected weight loss is maintained at the same level.

Issue 10: The clinical evaluator has recommended long term safety monitoring specifically involve vigilance for development of osteoporosis.

Response: Bone mineral density data from Study 12 do not indicate a negative effect of dapagliflozin on bone metabolism; 2 year data from this study will be available shortly. To confirm the absence of a causal connection with osteoporosis, the sponsor plans further evaluation of fractures in the proposed CV outcomes study.

Advisory committee considerations

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

The ACPM taking into account the submitted evidence of efficacy, safety and quality considered this product to have an overall *negative benefit-risk profile*.

[59] Larsen-Meyer, D. Enette, Newcomer,Bradley R Heilbronn, Leonie K et al. Effect of 6-Month Calorie Restriction and Exercise on Serum and Liver Lipids and Markers of Liver Function. Obesity 6 (16) 1355-1362.

In making this recommendation the ACPM considered the efficacy data were not balanced by appropriate evidence and management of safety risks, particularly in regard to genital and urinary tract infections; impaired renal and hepatic function and breast and bladder carcinoma. The ACPM advised that a major concern is the absence of clear data to reliably inform the assessment of the benefit-risk profile for this product.

The ACPM considered the Risk Management Plan (RMP) and advised that it was not able to be implemented at this time owing to lack of marketing in key jurisdictions and therefore was a poor mechanism to support the safe and effective use of this product for the proposed indication. As a result, it would be inappropriate to approve registration with the current RMP cited as a condition of registration. The ACPM recommended that as pre condition of future assessment of this application, the sponsor should provide a new RMP that has been developed and based on an evaluation of the additional safety data which has been considered by the Advisory Committee on the Safety of Medicines (ACSOM).

RMP

The ACPM highlighted its expectation that in addition to the above issues, the RMP should also be strengthened in the area of drug interactions (for example including non-steroidal anti-inflammatory drugs (NSAIDS)); and use in patients with hepatic impairment (such as clarity in the PI and supporting postmarket vigilance and education activities).

Finally the ACPM noted that the predominance of postmarket studies focussed on USA and EU populations. In the Australian context there is an anticipated higher use, proportionally, in Australian aboriginals, so it is critical that due consideration is given to the greater risk of specific adverse effects for this population group. This again, should be adequately addressed in the RMP.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of APPEBB dapagliflozin (as propanediol monohydrate) 10mg film coated tablets blister pack, AZ Dapagliflozin dapagliflozin (as propanediol monohydrate) 10 mg film coated tablets blister pack, BMS Dapagliflozinaz dapagliflozin (as propanediol monohydrate) 10 mg film, coated tablets blister pack, BMS/AZ Dapagliflozin dapagliflozin (as propanediol monohydrate) 10 mg film coated tablets blister pack, EDISTRIDE dapagliflozin (as propanediol monohydrate) 10 mg film coated tablets, blister pack, Empliciti dapagliflozin (as propanediol monohydrate) 10mg film coated tablets, blister pack and Forxiga dapagliflozin (as propanediol monohydrate) 10 mg film coated tablets bister pack, indicated for:

"Monotherapy

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.*

Initial combination

> *Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels).*

Add-on combination

Appebb, az, dapagliflozin, bms, edistride, empliciti, forxiga is indicated in patients with type 2 diabetes mellitus to improve glycemic control:

- *in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycemic control;*
- *in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycemic control;*
- *in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control."*

Specific conditions applying to these therapeutic goods

1. Details of the distribution of the drug including quantities and forms of products distributed and related batch numbers should be supplied on request while the drug remains on the ARTG.
2. The implementation in Australia of the dapagliflozin Risk Management Plan identified as the EU-RMP Version 4.1 (dated 17 April 2012) with the Australia Specific Annex (dated 17 April 2012), and any subsequent versions be imposed as a condition of registration with the following provisions:

- The implementation, prior to the supply of the product other than for purposes of a clinical trial or by way of advertisement to health care professionals, of an education program that:
  - includes an independent Continuing Professional Development, accredited medical education program (Category 1) and pre- and post- education assessment effectiveness
  - provides a focus on appropriate use, including patient selection and safety issues, and
  - has been agreed by OPR.
- The sponsor must provide details of a post marketing study strategy that is sufficiently powered to detect the adverse events of urinary tract infections, renal impairment, hepatic impairment, bone fractures, cancers in particular breast, bladder and prostate cancers, and to address if there are any progressive adverse long-term effects as a result of drug interactions. The final post marketing study strategy and protocol(s) must be agreed by the OPR prior to marketing.
- If a product familiarisation programme is undertaken the sponsor must put in place a process for collecting safety data that is approved by the OPR prior to programme launch.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Reference/Publication #