Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Empagliflozin

Proprietary Product Name: Jardiance

Sponsor: Boehringer Ingelheim Pty Ltd

January 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About 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

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area Under the Curve (concentration versus time) for time 0 to infinity
BMI	Body Mass Index
CI	Confidence Interval
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLP-1	Glucagon-Like Peptide 1
HDL	High Density Lipoprotein
HOMA-IR	Homeostasis Model Assessment index to assess Insulin Resistance
HbA1c	Glycosylated haemoglobin
HOMA-IS	Homeostasis Model Assessment index to assess Insulin Secretion
IC50	Half Maximal Inhibitory Concentration
LDL	Low Density Lipoprotein

Abbreviation	Meaning
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetics
QD	Once Daily
RMP	Risk Management Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT	Sodium-Glucose Linked Transporter
UGE	Urinary Glucose Excretion

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	17 April 2014
Active ingredient:	Empagliflozin
Product name:	Jardiance
Sponsor's name and address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Road North Ryde, NSW 2113
Dose form:	Film coated tablets
Strengths:	10 and 25 mg
Container:	Polyvinylchloride/Aluminium blister pack
Pack sizes:	10 and 30 tablets
Approved therapeutic use:	*Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:* *Monotherapy* *When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.* *Add-on combination therapy* *In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials)*.
Route of administration:	Oral
Dosage (abbreviated):	The recommended starting dose is 10 mg once daily. In patients tolerating 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. [Refer to the approved Product Information (PI; AusPAR Attachment 1) for full Dosage and Administration]
ARTG numbers:	208829 (10 mg) and 208827 (25 mg)

Product background

Empagliflozin is a selective and reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2) which is mainly expressed in the renal proximal tubules and accounts for approximately 90% of the glucose re-absorption. The inhibition of SGLT2 decreases the

renal re-absorption of glucose, thereby promoting glucose excretion in the urine resulting in reduction in blood glucose levels.

This AusPAR describes the application by Boehringer Ingelheim Pty Ltd (the sponsor) to register the new chemical entity empagliflozin (Jardiance) for the following indication:

> *as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.*

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 30 April 2014.

At the time the TGA considered this application, a similar application had been submitted to the US FDA (March 2013), European Medicines Agency (EMA) in the European Union (EU, March 2013), Switzerland (April 2013) and Canada (April 2013).

Product Information

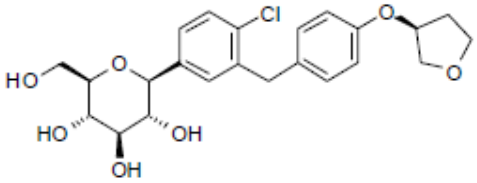
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

The drug substance (structure shown below) is a SGLT2 inhibitor and is manufactured by chemical synthesis. It is in the same class of compounds as canagliflozin and dapagliflozin. It is a white to yellowish powder. In aqueous media over the pH range 1.0-7.4, the drug substance is very slightly soluble. It is practically insoluble in toluene, sparingly soluble in methanol, slightly soluble in ethanol and soluble in 50% acetonitrile/water. It does not contain ionisable groups.

Figure 1: Structure of empagliflozin



There are no compendial monographs for the drug substance, but the specifications adopted for the material were acceptable.

Stability data regarding the drug substance was found to be acceptable.

Drug product

The product is an unscored immediate release film coated tablet containing 10 mg or 25 mg empagliflozin as the active ingredient, and the tablets have been formulated with conventional excipients. Both strengths of the tablet are to be packaged in polyvinyl chloride/Aluminium (PVC/Al) blister, in pack sizes of 10 (sample pack), or 30 tablets.

Formulation development of trial and the intended final formulations, process development as well as the final formulation and manufacturing process were carried out by the sponsor.

Tablet specifications including controls for appearance, identification, assay, degradation products, uniformity of dosage, dissolution and microbial purity have been evaluated.

Stability data (long term and accelerated stability conditions) on the finished product supported the assigned shelf life and storage conditions.

Biopharmaceutics

Three biopharmaceutic studies provided with this submission are summarised briefly below. Only one of these studies (Study U12-1744) has been assessed in detail as it included an analysis of the food effect and linearity on the pharmacokinetics (PK) of the proposed commercial formulation. The dossier included reports describing other bioavailability studies that examined the interaction of empagliflozin with other drug products. These studies have not been considered as part of this assessment.

Table 1: Biopharmaceutic studies

Study	Investigation	Objectives
U12-1744-01	Investigation of the effect of food on the bioavailability of a 25 mg empagliflozin tablet and assessment of dose proportionality between 10 mg and 25 mg empagliflozin tablets in an open, randomised, single dose, three period crossover study in healthy male and female subjects. (Study 1245.79)	The objectives of the trial were to investigate the effect of food on the bioavailability of a 25 mg empagliflozin final formulation (FF) tablet and to assess dose proportionality between 10 mg and 25 mg empagliflozin FF tablets under fasting conditions.
U08-1977-01	The effect of food on the bioavailability and PK of BI 10773 (empagliflozin) tablets, administered as a single dose of 50 mg with and without food to healthy male volunteers in an open label, randomised intra-individual crossover comparison design. (Study 1245.3)	To assess the food effect on PK and the extent of absorption of a single dose empagliflozin tablet trial formulation (TF) I (TF-I) in healthy subjects.
U11-1756-01	Relative bioavailability of 25 mg BI 10773 (empagliflozin) (FF) compared to 25 mg BI 10773 XX (TF II) following oral administration in healthy male and female volunteers (an open label, randomised, single dose, two way crossover study). (Study 1245.51)	To investigate the relative bioavailability of empagliflozin when administered as 25 mg empagliflozin FF compared with 25 mg empagliflozin TF-II.

The results from the studies above are summarised below:

- *Study 1245.3/U08-1977-01*: Administration of empagliflozin formulation with food resulted in a small decrease in empagliflozin exposure, with area under the concentration-time curve over time 0 to infinity ($AUC_{0-\infty}$) being 10% lower and the maximum plasma concentration (Cmax) being 29% lower under fed compared to fasted condition.
- *Study 1245.51/U11-1756-01*: This study demonstrated that empagliflozin formulations FF and TF-II are bioequivalent.
- *Study 1245.79/U12-1744-01*: Administration of empagliflozin formulation with food resulted in a decrease in empagliflozin exposure, with $AUC_{0-\infty}$ 16% lower and Cmax 37% lower under fed conditions compared with fasted conditions.

The company demonstrated a small but negligible difference in the dose proportionality, indicating that the products are virtually dose proportional between the 10 mg and 25 mg empagliflozin tablets.

A justification was provided for not conducting an absolute bioavailability study, for which the pharmaceutical chemistry aspects were deemed acceptable.

Advisory committee considerations

This submission was not presented for advice from the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

There are no outstanding issues from the quality evaluator's perspective, and approval can be recommended with respect to chemistry, manufacturing and control.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was generally high. All pivotal safety related studies were conducted under good laboratory practice conditions, with the exception of a number of safety pharmacology studies. The relevant EU guideline (CHMP/ICH/423/02[1]) specifies that such studies should be conducted according to good laboratory practice conditions. However, the studies were well documented nevertheless and this is not considered a major concern.

Pharmacology

Primary pharmacology

Empagliflozin is a SGLT2 inhibitor. Following glomerular filtration, glucose is reabsorbed back into the circulation from the proximal tubules of the kidney[2]. SGLT2 is expressed in the proximal segment of the renal tubules where it is responsible for the majority of renal

[1] European Medicines Agency (EMA). CHMP/ICH/423/02. Note for guidance on the nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals.
[2] Wright EM, Hirayama BA and Loo DF. Active sugar transport in health and disease. *J. Intern. Med* 2007;61:32-43.

glucose reabsorption[3]. The renal reabsorption of glucose is virtually complete under physiological conditions; almost no glucose appears in the urine (< 0.5 g/day). Inhibition of SGLT2 results in increased urinary glucose excretion (UGE), leading to lowered plasma glucose.

Glucose from digested food is absorbed via SGLT1, which is located to the apical epithelium of the small intestine. SGLT1 also contributes to renal glucose reabsorption, but to a lesser degree than SGLT2.

In vitro, empagliflozin inhibited human SGLT2 transport with nanomolar potency. The half maximal inhibitory concentration (IC_{50}) of approximately 1.5 nM compares favourably with the clinical free concentration at lowest (C_{trough}) level of 1.7 nM (for a 10 mg dose) (assuming 10% free fraction). Empagliflozin had low inhibitory activity on human SGLT1 (IC_{50} > 6 μM). Therefore, empagliflozin is not expected to inhibit systemic SGLT1. Local concentrations in the gastrointestinal tract, where SGLT1 is also expressed, will be much higher though (222 μM, based on a 25 mg tablet in 250 mL liquid). The three major human empagliflozin metabolites, empagliflozin 2-O-glucuronide, 3-O-glucuronide and 6-O-glucuronide, did not show significant inhibition of SGLT2 (IC_{50} approximately 1 μM), and are therefore not expected to contribute to clinical efficacy.

Empagliflozin had similar potency against the mouse, rat and human SGLT2 isoforms, thus supporting the use of the rodent species in toxicity studies, based on pharmacological considerations. No information was provided regarding the activity at the SGLT2 transporter from dogs, the non-rodent species used in toxicity studies. However, given that significantly increased UGE was seen, empagliflozin was clearly pharmacologically active in dogs. Low inhibitory activity was seen on SGLT1 from mice (IC_{50} 28 μM). However, empagliflozin appeared to have approximately 80 times higher inhibitory activity at this transporter from rats. Therefore, off-target effects on this transporter may have been seen in rats at lower doses than would occur in mice.

The in vivo efficacy of empagliflozin was tested in two standard animal models of diabetes (Zucker Diabetic Fatty (ZDF) rat and db/db diabetic mice) as well as in a rat model of diet induced obesity and in normoglycaemic dogs. As expected based on its pharmacological action, a single oral dose of empagliflozin increased UGE in all tested animal species. There was also a coincident reduction in postprandial blood glucose levels. The half maximal effective dose (ED_{50}) for blood glucose lowering was 0.6 mg/kg in diabetic rodents (1.8 to 3.6 mg/m^2), while the ED_{50} for increased urinary excretion in normoglycaemic dogs was 0.9 mg/kg (18 mg/m^2). The efficacious doses support the proposed clinical dose of 10 to 25 mg/day (6.6 to 16.5 mg/m^2). Obese or diabetic rats that received repeated daily doses of empagliflozin for up to 5 weeks had improved glucose tolerance, lower fasting glucose levels, lower glycosylated haemoglobin (HbA1c) levels and lower insulin levels than their untreated counterparts. There was no evidence of hypoglycaemia. Reduced body fat and reduced body weight gain were seen in obese rats that received ≥ 3 mg/kg/day PO empagliflozin. Overall, the animal studies support the proposed monotherapy indication and the proposed clinical dose.

Pharmacodynamic drug interactions

Combinations of empagliflozin with other antidiabetic agents (metformin, exenatide, insulin, pioglitazone, glipizide, linagliptin and voglibose) were assessed for efficacy in diabetic rats (animal model of type 2 diabetes). While each agent alone effectively lowered postprandial glucose levels, the combination of empagliflozin with each of the other antidiabetics was significantly more effective, with mainly an additive effect. In general,

[3] Jabbour SA and. Goldstein BJ. Sodium glucose transporter 2 inhibitors: blocking renal tubular reabsorptionof glucose to improve glycaemic control in patients with diabetes. *Int J Clin Practice.* 2008;62:1279-1284.

the efficacious doses were similar to the maximum clinical doses for each of the agents (on a body surface area basis)[4]. Therefore, the pharmacodynamic (PD) drug interaction studies support the combined use of empagliflozin/metformin, empagliflozin/exenatide (a glucagon-like peptide 1 (GLP-1) receptor agonist), empagliflozin/insulin, empagliflozin/linagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor), empagliflozin/pioglitazone (a thiazolidinedione), empagliflozin/glipizide (a sulfonylurea) and empagliflozin/voglibose (an α-glucosidase inhibitor). Triple therapy was not examined.

Secondary pharmacodynamics and safety pharmacology

Empagliflozin had low inhibitory activity at other sugar transporters: glucose transporter 1 (GLUT1), sugar transporter 4 (SGLT4), SGLT5 and SGLT6 (IC_{50} ≥ 1.1 μM; 16 times the clinical free Cmax). Empagliflozin (at 10 μM; 146 times the clinical free Cmax levels) did not show significant activity against a range of receptors, ion channels and enzymes. Therefore, no off-target activities are predicted at the proposed clinical dose.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal systems as well as effects on kidney and liver function. CNS and respiratory function were unaffected in rats at ≥ 2000 mg/kg PO (estimated Cmax 66.4 μM[5]; 97 times the clinical Cmax). In vitro, there was no effect on human ether-a-go-go related gene potassium channel (hERG K+) tail current or action potential duration in isolated guinea pig papillary muscles at ≤ 10 μM (approximately 146 times the free clinical Cmax). No electrocardiogram (ECG) abnormalities were observed in dogs that received ≤ 100 mg/kg PO empagliflozin (estimated Cmax 80.2 μM[6]; 117 times the clinical Cmax). Therefore, QT prolongation[7] is not predicted during clinical use.

Increased gastric emptying without any effects on gastrointestinal transit was observed in rats that received 30 mg/kg PO empagliflozin (exposure ratio based on Cmax (ER_{Cmax}), 1.5). Given the low margin, this is considered clinically relevant but not expected to be adverse.

As expected based on its mechanism of action and consistent with others in its class, empagliflozin treatment affected renal parameters: increased UGE was seen at all tested doses in rats (≥ 3 mg/kg) with increased urinary excretion of sodium and chloride observed at higher doses (≥ 10 mg/kg). Increased urinary volume and glucosuria were consistently seen in treated animals in the toxicity studies. The urinary findings would be expected during clinical use.

Overall, effects on CNS, cardiovascular and respiratory function are not predicted during clinical use, some minor gastrointestinal changes may be experienced and increased urination and excretion of glucose would be expected.

[4] Efficacious doses in rats were 3 mg/kg empagliflozin (18 mg/m^2), 300 mg/kg metformin (1800 mg/m^2), 0.01 mg/kg exenatide (0.06 mg/m^2), 10 mg/kg pioglitazone (60 mg/m^2), 1 mg/kg linagliptin and glipizide (6 mg/m^2). The maximum clinical doses are 25 mg empagliflozin (16.5 mg/m^2), 30 mg pioglitazone (19.8 mg/m^2), 2000 mg metformin hydrochloride (1030 mg/m^2 metformin base), 20 μg exenatide (0.013 mg/m^2), 5 mg linagliptin and glipizide (3.3 mg/m^2).

[5] Based on data in Study U08-3183-01. Cmax for a 1000 mg/kg dose was 33.2 μM.

[6] Based on data in Study U10-3252-01. Day 1 data, average male and female.

[7] The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.

Pharmacokinetics

Absorption

Empagliflozin was generally rapidly absorbed by the oral route in mice, rats, dogs and humans (< 3 h). Oral bioavailability was moderate to low in rats (approximately 32%) and high in mice and dogs (89 to 97%). After a single intravenous (IV) dose, the plasma half-life was between 0.6 and 3.6 h in mice and rats and approximately 6 h in dogs. Following oral dosing, the apparent half-life was similar across species (mice, rats, dogs and humans) (4 to 8 h). Exposures (AUC) were generally dose proportional in animal species (mice, rats and dogs) and there was no evidence of accumulation with repeat dosing. Empagliflozin exposures were generally greater in female mice compared to their male counterparts, which correlated with greater metabolism and faster clearance seen in males. There were no consistent sex differences in rats and dogs, though at higher doses, female rats tended to have higher exposures (AUC) than their male counterparts.

Distribution

Plasma protein binding by empagliflozin was moderate (82 to 91%) in all species (mouse, rat, dog, rabbit, and human) and independent of concentration across the range tested including a clinically relevant concentration. Binding was largely attributed to albumin. Partitioning into blood cells was moderate in rat, dog and human ($C_{blood\ cell}/C_{plasma}$ ratio approximately 0.3). The volume of distribution was similar to or slightly greater than total body water in mice, rats, dogs and humans. Tissue distribution in pigmented rats after PO administration of radiolabelled empagliflozin was limited, highest concentrations were observed in the gastrointestinal tract and organs associated with excretion. Empagliflozin related radioactivity was low to undetectable in brain tissues. Radiolabelled (^{14}C)-empagliflozin derived radioactivity was not associated with the melanin containing tissues in the eye or skin, and was not detected in testes, lens of the eye, or bone marrow at any sampling time.

Metabolism

Turnover of ^{14}C-empagliflozin in hepatocytes and liver microsomes was shown to be low, suggesting that empagliflozin is not metabolised to any great extent by cytochrome P450 (CYP) enzymes. In humans, the primary route of metabolism was glucuronidation with 3 notable glucuronide metabolites (empagliflozin 2-O-glucuronide, 3-O-glucuronide and 6-O-glucuronide). In vitro studies indicated a major role of uridine 5'-diphospho-glucuronosyltransferase (UGT) 2B7 in the formation of empagliflozin 2-O-glucuronide and UGT1A3, 1A8 and 1A9 in the formation of empagliflozin 3-O-glucuronide. The UGT involved in the formation of empagliflozin 6-O-glucuronide has not been identified. Given that UGT1A3, 1A8, 1A9 and 2B7 are known to be expressed in the kidney or gastrointestinal tract (as well as the liver)[8], the formation of these glucuronides is likely to occur, at least in part, extrahepatically. While oxidation was the primary route of metabolism in the mouse, rat, and dog, the three glucuronides were each formed in at least one of these animal species. There were no significant human specific metabolites. The human metabolite profile was considered sufficiently represented in the animal species for mice, rats and dogs to serve as good models in the toxicology studies.

[8] Kiang TKL et al. UDP-glucuronosyltransferases and clinical drug-drug interactions. *Pharmacol. Ther.* 2005; 106: 97-132.

Excretion

Excretion of empagliflozin and/or its metabolites was predominantly via the faeces in rats (PO, IV) and dogs (PO, IV) and via both the faeces and urine in mice (low dose, PO) and humans (PO). At high oral doses, a higher proportion of radioactivity was excreted in the faeces of mice and rats, suggesting saturation of absorption. Biliary excretion was demonstrated in rats.

Conclusion on PK

The PK profile in mice, rats and dogs was considered sufficiently similar to that of humans to allow these animal species to serve as an appropriate model for the assessment of empagliflozin toxicity in humans.

Pharmacokinetic drug interactions

Metabolism of empagliflozin does not involve CYP450 enzymes. In vitro, empagliflozin (≤ 100 μM; 1456 times the clinical free Cmax) had no significant inhibitory activity on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4, and there was no significant induction of CYP1A2, 2B6 or 3A4 activity or messenger ribonucleic acid (mRNA) levels at ≤ 30 μM (437 times the clinical free Cmax). Therefore, PK drug interactions involving CYP450 enzymes are not expected to occur clinically. While empagliflozin had some inhibitory activity on UGT1A1, there is a sufficient margin for this to be considered not clinically relevant (no inhibitory activity at 16.7 μM; 243 times the clinical free Cmax).

Empagliflozin was shown to be a substrate of P-glycoprotein and breast cancer resistance protein (BCRP). However, the high oral bioavailability of empagliflozin (at least in mice and dogs; ≥ 89%) suggests that these transporters do not have a significant effect on the absorption of empagliflozin, and inhibitors of these transporters are unlikely to significantly affect the systemic exposure to empagliflozin. Empagliflozin was also a substrate of organic anion transporter 3 (OAT3), OATP1B1 and OATP1B3. Therefore, inhibitors/inducers of these transporters may affect the disposition of empagliflozin. Empagliflozin was not a substrate of OAT1 or OCT2. No clinically relevant inhibitory activity was observed at P-glycoprotein, OAT3, OATP1B1, OATP1B3, OATP2B1, BCRP or multidrug resistance associated protein 2 (MRP2); IC50 values > 650 times the clinical free Cmax). Therefore, empagliflozin is not expected to alter the PK of drugs that are substrates of these transporters.

In summary, PK drug interactions involving CYP450 enzymes are unlikely. Inhibitors/inducers of OAT3, OATP1B1 and OATP1B3 could potentially alter the in vivo disposition of empagliflozin.

In vivo drug interactions were assessed with empagliflozin/metformin and empagliflozin/linagliptin combinations in rats. No consistent interactions were evident with empagliflozin and metformin. Exposures to empagliflozin were higher (1.2 to2 times) when provided in combination with linagliptin, and linagliptin exposures tended to be lower (30 to 70% lower) when this drug was supplied in combination with empagliflozin. The draft PI document states that linagliptin had no effect on the PK of empagliflozin in human subjects. Therefore, the PK drug interactions seen in rats with empagliflozin and linagliptin do not appear to be clinically relevant.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice and rats, using animals of both sex, the clinical (PO) and a parenteral route (mice only), and an observation period of 15 days, in accordance with the EU guideline on single dose toxicity (3BS1a)[9]. Maximum non-lethal doses by the oral route were the maximum tested dose (2000 mg/kg) in mice and rats, while the maximum non-lethal dose by the intraperitoneal (IP) route was 300 mg/kg in mice. Deaths were seen at the highest IP dose of 2000 mg/kg. Clinical signs (abnormal gait, yellow staining of the fur, soft stool/loose faeces and poor grooming) were observed in both species after PO dosing (all tested doses; 2000 mg/kg in mice and ≥ 300 mg/kg in rats) and in mice after IP dosing (at the highest tested dose, 2000 mg/kg). Gross pathological examination revealed no notable effects after oral administration. In deceased female mice that received IP doses of empagliflozin, fluid filled intestines (red) was the only finding. Empagliflozin was considered to have a low order of acute oral toxicity.

Repeat dose toxicity

Studies by the oral route were conducted in mice (up to 13 weeks duration), rats (up to 26 weeks) and dogs (up to 52 weeks). The duration of the pivotal studies (rat and dog), the species used, group sizes and the use of both sexes were consistent with ICH International Conference on Harmonisation of Technical Requirements (ICH) guidelines. Dose selection in the pivotal studies was appropriate based on high relative exposures (compared to the maximum clinical dose) achieved. The limit dose was used in the mouse studies, while up to the limit dose was used in a 4 week rat study.

Table 2: Relative exposure in oral repeat dose toxicity and carcinogenicity studies

Species	Study duration	Dose (mg/kg/day)	Sex[#]	$AUC_{0-24\,h}$ (µM·h)	Exposure ratio[##]
Mouse (CD-1)	13 weeks	500	M	130	27
			F	364	77
		750	M	225	47
			F	320	68
		1000	M	294	62
			F	468	99
	Approximately 2 years (carcinogenicity)	100	M	20.7	4
			F	32.7	7
		300	M	51.7	11

[9] International Conference on Harmonisation of Technical Requirements (ICH) Topic 3BS1a. Single dose toxicity.

Species	Study duration	Dose (mg/kg/day)	Sex[#]	$AUC_{0-24\,h}$ (µM·h)	Exposure ratio[##]
			F	135	28
		1000	M	211	45
			F	296	62
Rat (Wistar)	26 weeks	30	M	11.2	2
			F	26.0	5
		100	M	47.4	10
			F	87.8	19
		700	M	166	35
			F	372	78
	2 years (carcinogenicity)	100	M	79.8	17
			F	100	21
		300	M	122	26
			F	214	45
		700	M	197	42
			F	340	72
Dog (Beagle)	52 weeks	10	M/F	85.9	18
		30	M/F	250	53
		100	M/F	1140	241
Human (Type 2 diabetes patients)	28 days steady state (Study number U09-1970)	(25 mg)	M+F	4.74	–

[#]M = male, F = female. [##]Animal:human plasma $AUC_{0-24\,h}$.

Major toxicities

In general, the toxicity profile of empagliflozin was similar to others in the pharmacological class with effects associated with the primary pharmacology of the drug (glucosuria, osmotic diuresis, effects on body weight and food consumption), secondary effects associated with SGLT2 inhibition (changes in the liver, pancreas and adrenals, other clinical chemistry changes and the risk of urinary tract infections (UTIs)) or off-target effects on SGLT1 (gastrointestinal toxicity, effects on bone production and vascular

mineralisation). Additional findings not seen with others in the pharmacological class, included additional effects on the kidneys of male mice.

Effects associated with the primary pharmacology

As with other members of the pharmacological class, empagliflozin induced glucosuria and an osmotic diuretic effect in all species examined. Dehydration was only seen in dogs that received 100 mg/kg/day PO empagliflozin (exposure ratio based on AUC (ER_{AUC}), 241). Water consumption was not monitored in the toxicity studies, but animals that received empagliflozin are likely to have drunk more water. Reduced body weight gain was observed in both rats (≥ 30 mg/kg/day; ER_{AUC} 2 (male data)) and dogs (≥ 10 mg/kg/day; E_{RAUC} 18), but not mice. However, a significant increase in food consumption was observed in the latter species. Dogs with very high exposures to empagliflozin (at 100 mg/kg/day for 52 weeks; ER_{AUC} 241) had a thin appearance and the effect on weight gain was considered adverse, necessitating food supplementation. The no observed effect level (NOEL) for effects on body weight was not established. Effects on body weight may be seen in patients.

Effects secondary to SGLT2 inhibition

Following chronic use, there were clinical chemistry and histopathological signs that animals were moving towards a catabolic state. Increased blood urea nitrogen (associated with protein catabolism), increased serum triglycerides (lipid mobilisation) and an increased level of urinary ketones were seen in both rats (≥ 30 mg/kg/day; ER_{AUC} 2 (male data)) and dogs (various doses ≥ 30 mg/kg/day; ER_{AUC} 53). Mild increases in liver enzymes (< 2 fold) were seen in rats (≥ 30 mg/kg/day; no NOEL) and dogs (≥ 10 mg/kg/day; no NOEL) (serum chemistry parameters not examined in mice), while hepatocyte vacuolation was evident during post-mortem analyses in all species: mice at ≥ 100 mg/kg/day (ER_{AUC} 4 (male data); no NOEL), rats at ≥ 30 mg/kg/day (ER_{AUC} 2 (male data)) and dogs at ≥ 30 mg/kg/day (ER_{AUC} 53; NOEL 10 mg/kg/day). These changes are consistent with a mobilisation of lipid, a decrease in glycogen storage and an induction of gluconeogenesis: all secondary effects of chronic glucose loss. Acinar epithelial vacuolation (zymogen depletion) in the pancreas of rats that received ≥ 100 mg/kg/day PO empagliflozin (NOEL 30 mg/kg/day; ER_{AUC} 2 (male data)) was considered to be secondary to the effects on body weight and food consumption. No pancreatic lesions were observed in mice or dogs. None of the above effects are considered to be a safety concern during clinical use.

Chronic administration of empagliflozin to rodents led to several changes in the kidney and urinary tract which are consistent with findings seen with others in the pharmacological class. These included kidney cortical tubule dilatation in rats at ≥ 100 mg/kg/day (ER_{AUC} 19) and pelvic, ureter and urinary bladder dilatation in male mice at ≥ 100 mg/kg/day (ER_{AUC} 4). A NOEL was not established in the long term studies. These urinary tract changes are thought to be adaptive and associated with the increased urinary output and workload associated with the elimination of increased amounts of glucose.

As with other members of the pharmacological class, the increased glucose levels in urine may predispose recipients to UTIs. In the animal studies, evidence of UTIs (for example, inflammatory reactions) was seen in some animals. Chronic interstitial nephritis was seen in dogs that received 100 mg/kg/day empagliflozin (NOEL 30; ER_{AUC} 53). Therefore a risk for UTIs exists in patients.

An increased incidence and severity of vacuolation of the zona glomerulosa of the adrenal gland of rats (≥ 30 mg/kg/day; ER_{AUC} 2; no NOEL) and dogs (≥ 30 mg/kg/day; NOEL 10 mg/kg/day; ER_{AUC} 18) was associated with empagliflozin treatment. Effects on the adrenal gland were reversible when treatment was terminated. Adrenal effects may be associated with the physiological response to the polyuria induced volume depletion which would stimulate adrenal aldosterone synthesis via the renin-angiotensin-aldosterone system.

This is supported by the finding that increased aldosterone levels were also reported in individuals with mutations in *SLC5A2* (the gene encoding SGLT2)[10].

Off-target effect on SGLT1

Consistent with others in the class, gastrointestinal disturbances (soft faeces/diarrhoea, swollen abdomen and/or glandular stomach erosion/ulcer), effects on bone (increased trabecular bone and increased serum levels of bone alkaline phosphatase (ALP)) and multi-organ mineralisation were seen in rats and/or dogs. These effects are all consistent with (off-target) SGLT1 inhibition in the intestine, resulting in glucose malabsorption, thereby promoting gastrointestinal bacterial growth which results in a reduction in pH, which in turn facilitates an increase in calcium absorption from the gastrointestinal tract. The gastrointestinal disturbances are consistent with glucose malabsorption, while the bone effects and multi-organ mineralisation are consistent with hypercalcaemia. Renal mineralisation in rats was often observed in the absence of overt hypercalcaemia, but increased urinary output (and hence increased excretion of calcium) was always evident. These signs of SGLT1 inhibition were seen at ≥ 30 mg/kg/day PO in rats (60 times the clinical dose on a mg/kg basis) and ≥ 10 mg/kg/day PO in dogs (20 times the clinical dose). A NOEL was not established in either species. Mice appeared to be less sensitive to this phenomenon: there was minimal evidence of SGLT1 inhibition, with abdominal swelling only observed at very high doses (≥ 300 mg/kg/day; NOEL 100 mg/kg/day, 200 times the clinical dose). While empagliflozin had inhibitory activity against both mouse and rat SGLT1, the potency was 80 times higher for this transporter from rats compared to mice, thus explaining the reduced sensitivity in the latter species. No information was provided regarding inhibitory activity against SGLT1 from dogs. Empagliflozin had approximately 4.5 times higher potency against human SGLT1 than mouse SGLT1. Given the NOEL in mice is 200 times the clinical dose, SGLT1 inhibition and its side effects are not expected to occur in patients.

Additional renal effects not seen with others in the pharmacological class

A constellation of renal lesions was seen in male mice, but not their female counterparts, and no such lesions were seen in rats or dogs. These changes included single cell necrosis, tubular atrophy, tubular karyomegaly, tubular hypertrophy, cysts, cystic tubular hyperplasia and atypical tubular hyperplasia. Increased mitosis was seen in areas with hyperplastic changes, and kidney tumours (tubular adenomas and carcinomas) developed in the long term study (see *Carcinogenicity*). The mechanism underlying the kidney damage in male mice is not associated with the pharmacological action of the drug. (No such findings have been seen with other SGLT2 inhibitors). The sponsor has postulated a cycle of degeneration/regeneration leading to the lesions observed. The histopathological findings support such a scenario. A number of studies were submitted to elucidate the mechanism underlying the initial degenerative process and to attempt to explain the species and gender specific effects. Greater oxidative metabolism of empagliflozin occurs in the kidney of male mice compared to their female counterparts. One particular metabolic pathway predominates with metabolites found up to 7 times those seen in the kidneys of females. Metabolites from this pathway are cytotoxic and/or genotoxic and their involvement in renal lesion formation is plausible. These metabolites are formed at lower levels in female mice and rats (both sexes) and no degenerative lesions were seen in these species, suggesting a threshold exists for genotoxicity/cytotoxicity in vivo. A NOEL was not established for kidney damage in male mice (Lowest observed adverse effect level (LOEL) 100 mg/kg/day; ER_{AUC} 4). Exposures at the NOEL in female mice, rats and dogs are reasonably high, ranging from 40 to 240 times the clinical AUC. As the metabolic pathway leading to the formation of cytotoxic/genotoxic metabolites does not appear to occur in

[10] Calado J et.al. Familial renal glucosuria: SLC5A2 mutation analysis and evidence of salt-wasting. *Kidney Int*. 2006; 69: 852-855.

humans, and reasonable safety margins exist in female mice, rats and dogs, the clinical relevance of the degenerative renal lesions is considered low.

An exacerbation of chronic progressive nephropathy (CPN) was also seen in male mice that received 1000 mg/kg/day empagliflozin (NOEL 300 mg/kg/day; ER_{AUC} 11). CPN exacerbation, at least in rats, can occur as a result of alterations in the diet, in renin angiotensin levels and/or filtration alterations[11], and is not considered to be an indicator of nephrotoxicity or kidney tumour development in human subjects[12]. It is unclear if this also applies to CPN in mice. Exacerbation of CPN was not seen in rats treated with empagliflozin, though in general, lower exposures were seen in this species. A role, if any, of CPN in the additional renal lesions in male mice is unknown. Nonetheless, the exacerbation of CPN on its own is not considered to be clinically relevant.

A reduction in pH was sometimes (but not always) observed in rats (2 and 4 week studies) and dogs (13 week study) (urinalysis parameters were not assessed in mice). The underlying cause for the pH reduction is unknown.

Other effects

Follicular cell hypertrophy was seen in the thyroid of male rats that received ≥ 30 mg/kg/day empagliflozin for 26 weeks. There were no other thyroid findings in any other species or any other study in rats. Therefore, the thyroid changes are not considered significant.

Some changes in red blood cell (RBC) parameters (decreased haematocrit, haemoglobin and/or RBCs) were occasionally seen in rats given ≥ 30 mg/kg/day PO empagliflozin (no NOEL), with females affected to a greater extent. The changes were not always significant or consistent and such effects were not seen in mice or dogs, suggesting these findings may have minimal clinical significance.

Combination studies

Repeat dose toxicity studies of up to 13 weeks duration were conducted with empagliflozin/metformin and empagliflozin/linagliptin combinations to rats. The clinical route (PO) was used in all studies. Rats are considered an appropriate species to assess the toxicity of empagliflozin and are a species that has been used previously to assess the toxicity of both linagliptin and metformin. Parallel single agent groups were included in the pivotal studies. Not all combination groups were subject to detailed post-mortem analyses.

The dose ratios of empagliflozin to linagliptin were 2:1 and 5:1, corresponding well with the clinical dose ratio[13]. No new or exacerbated toxicities were observed with the combination of empagliflozin and linagliptin, when taking into account the higher empagliflozin exposures when provided in this combination. The toxicities observed with empagliflozin/linagliptin combinations were clearly dominated by empagliflozin, but this is anticipated given the lower toxicity of linagliptin. Exposures at the no observed adverse effect level (NOAEL; 30/15 mg/kg/day PO empagliflozin/linagliptin) were 5 and 9 times the AUC at the maximum clinical doses of empagliflozin and linagliptin[14], respectively.

Dose ratios of empagliflozin to metformin were 1:2 in both studies, which differs from the clinical dose ratio of 1:15.6 to 1:62.48. Additive or exacerbated effects with the

[11] Hard GC, Johnson KJ, and Cohen SM. A comparison of rat chronic progressive nephropathy with human renal disease - implications for human risk assessment. *Critical Rev Toxicol*. 2009;39(4):332-346.
[12] Melnick RL et al. Chemically exacerbated chronic progressive nephropathy not associated with renal tubular tumor induction in rats: an evaluation based on 60 carcinogenicity studies by the National Toxicology Program. *Toxicol Sci*. 2012;128:346-356.
[13] Clinical dose ratios based on a once daily dose of 25 mg for empagliflozin, 390-1560 mg for metformin (corresponding to 500-2000 mg metformin hydrochloride) and 5 mg linagliptin.
[14] Clinical AUC of 158 nM.h for a 5 mg linagliptin dose (from a previous submission).

combination (compared to either agent alone) included: effects on some RBC parameters (increased haematocrit), increased serum triglyceride (associated with an enhanced effect on lipid mobilisation), hypochloraemia, depressed thymic weights and increased liver and kidney weights with increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The effects on the liver (and liver enzymes) are consistent with an additive effect on lipid mobilisation and glycogen storage. There appeared to be an increased incidence of pelvic epithelial mineralisation in the kidneys of animals that received the combination of 200/400 mg/kg/day PO empagliflozin/metformin. Mineralisation observed with empagliflozin alone is thought to be associated with increased calcium absorption as a result of SGLT1 inhibition and is not thought to be clinically relevant. How metformin may affect this change is unclear. The NOAEL was considered to be 100/200 mg/kg/day PO empagliflozin/metformin (based on the 2 week study). Exposures at these doses were reasonable: 13 and 2.7 times clinical AUC at the maximum clinical dose of empagliflozin and metformin[15], respectively.

Genotoxicity

The potential genotoxicity of empagliflozin was investigated in the standard battery of tests: bacterial reverse mutation assays, in vitro mouse lymphoma tk assays and in vivo rat (Sprague Dawley and Wistar) bone marrow micronucleus assays. The conduct of the studies was in accordance with ICH guidelines. Concentrations/doses used were appropriate (up to maximum recommended levels or limited by cytotoxicity), a suitable set of *Salmonella typhimurium* and *Escherichia coli* strains was used in the bacterial gene mutation assay, and the assays were appropriately validated. Negative results were returned in all assays, empagliflozin was concluded to be not genotoxic.

Carcinogenicity

The carcinogenic potential of empagliflozin by the oral route was investigated in 96 to 104 week studies in mice and rats. Group sizes were appropriate and suitable dose levels were selected, resulting in > 25 times the clinical AUC at the highest dose (ICHS1C(R2))[16]. Survival was unaffected in rats and female mice but reduced survival was seen for male mice receiving the high dose (1000 mg/kg, ER_{AUC} 45), necessitating the early termination of this group (in week 97). This is not considered to critically impact the reliability of the mouse study since these events occurred late in the overall course of the study. An increased incidence of renal atypical tubular hyperplasia, renal tubular adenomas and carcinomas was seen in male mice at 1000 mg/kg/day (ER_{AUC} at the NOEL, 11). These kidney preneoplastic and neoplastic changes appeared to occur in a background of degenerative renal changes (single cell necrosis, tubular atrophy). The sponsor has proposed that the kidney tumours have arisen due to a cycle of epithelial cell injury leading to an adaptive response of proliferative repair and ultimately neoplasia. This is considered a possible scenario. There were no preneoplastic or neoplastic lesions seen in the kidney of treated female mice (≤ 1000 mg/kg/day; ER_{AUC} 62), rats (≤ 700 mg/kg/day; ER_{AUC} at least 42) or dogs (≤ 100 mg/kg/day; ER_{AUC} 241), suggesting these tumours may have a low clinical relevance. The sponsor provided studies to elucidate the underlying mechanism for the degenerative lesions in male mice specifically. These are discussed in the *Repeat dose toxicity* section. As the cytotoxic/genotoxic metabolite(s), which likely contribute(s) to the renal damage/proliferative tubular lesions, are not formed in humans and acceptable margins exist for tumour formation in both mice and rats (margins would

[15] Clinical AUC of 159 μM·h for a 2000 mg metformin hydrochloride dose (Timmins P et al. Steady state pharmacokinetics of a novel extended release metformin formulation. *Clin Pharmacokinet.* 2005;44:721-729).
[16] ICH Topic S1C(R2) Dose selection for carcinogenicity studies of pharmaceuticals.

be even higher than those cited above for the standard clinical dose of 10 mg), the renal tubular tumours are considered to have low clinical relevance.

The incidence of haemangioma of the mesenteric lymph node (18%) was statistically significantly increased in male rats given 700 mg/kg/day PO empagliflozin (ER_{AUC} 42) and was considered related to treatment. There was no treatment related increase in the incidence of malignant vascular tumours. The underlying cause of the benign blood vessel tumours is not known. However, given the reasonable safety margins (NOEL 300 mg/kg/day for males (ER_{AUC} 26) and 700 mg/kg/day for females (ER_{AUC} 72)), the clinical relevance of this finding is considered to be low.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre-/postnatal development). Numbers of animals and the timing/duration of treatment were appropriate. All studies were conducted by the oral route. Toxicokinetic data were obtained either from animals in the studies or from similarly-treated animals in accompanying studies. Exposure levels for empagliflozin were significantly greater than the clinical exposure from a 25 mg dose (Table 3).

In rats, fertility was unaffected when empagliflozin treated males were paired with treated females (NOEL 700 mg/kg/day; ERAUC 155). Effects on fertility are not predicted during clinical use.

Table 3: Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µM·h)	Exposure ratio#
Rat (WI(Han))	Fertility *toxicokinetics from pilot study*	100	102	22
		300	228	48
		700	734	155
	Embryofetal development *toxicokinetics from pilot study*	100	102	22
		300	228	48
		700	734	155
Rabbit (NZW)	Embryofetal development *toxicokinetics from pilot study*	100	191	40
		300	608	128
		700	659	139
Rat (WI(Han))	Pre-/postnatal development	10	6.55	1.4
		30	19.7	4
		100	76.6	16

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (µM·h)	Exposure ratio#
Human (type 2 diabetes patients)	Steady state (U09-1970)	[25 mg]*	4.74	–

= Animal:human plasma $AUC_{0\text{-}24\ h;}$ *daily dose 25 mg = 0.5 mg/kg for a 50 kg patient.

Empagliflozin was shown to cross the placenta in rats only at very low levels with low to undetectable levels of drug related material observed in the fetus (≤ 10% of maternal plasma levels). In rats, an increased incidence of the skeletal malformation, bent limb bones, was observed in fetuses of dams given 700 mg/kg/day empagliflozin (NOEL 300 mg/kg/day; ER_{AUC} 48) while an increased incidence of embryofetal lethality was seen in rabbits at this dose (NOEL 300 mg/kg/day; ER_{AUC} 128). These adverse embryofetal effects occurred in the context of maternotoxicity and are not considered a direct drug related effect. Given the large safety margins at the NOEL, these adverse embryofetal effects are not considered a concern during clinical use. However, the developing kidney has been identified as a target for irreversible changes in studies in rats conducted with other SGLT2 inhibitors (Dapagliflozin AusPAR; Canagliflozin Food and Drug Administration (FDA) report) and the same may be expected for empagliflozin (see below).

Empagliflozin and/or its metabolites were readily excreted into the milk of lactating rats with concentrations 1.5 fold maternal plasma concentrations. However, empagliflozin was undetectable in the plasma of breast-fed pups. In a pre/postnatal development study in rats, impairment of pup development was observed in the form of decreased pup weights (in offspring of dams given ≥ 30 mg/kg/day empagliflozin; NOEL 10 mg/kg/day; ER_{AUC} 1.4) and transient deficits in learning and memory that were observed in male pups (only) of dams treated with 100 mg/kg/day (NOEL 30 mg/kg/day; ER_{AUC} 4).

Reduced postnatal weight gain has been seen in pups treated with other SGLT2 inhibitors and in SGLT2-knockout animals, suggesting some pharmacological activity in these pups. At necropsy, renal pelvic dilatation was observed in some breast fed pups. Though there was no clear dose response, this kidney change has been observed in breast fed pups of dams given another SGLT2 inhibitor and in juvenile animals treated directly with other SGLT2 inhibitors (Dapagliflozin AusPAR; Canagliflozin FDA report), and the finding should be considered to be related to treatment. The findings may be associated with the reduced ability of the developing kidney to handle the increased urinary output induced by the drug. Kidney anatomical maturation occurs postnatally in rats, with nephrogenesis continuing to 11 days from birth [17] and tubular differentiation continuing until the time of weaning (approximately 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[18] . As such, the finding of irreversible kidney changes in rat pups suggests a risk to renal development in humans during gestation and the first 2 years of life.

Given its excretion into milk and the possibility of adverse effects on the growth and development of breast fed infants, empagliflozin should not be used by women who are breastfeeding. Further, empagliflozin should not be taken during pregnancy.

[17] Kavlock RJ and Gray JA. Evaluation of renal function in neonatal rats. Biol. Neonate 1982; 41:279-288.
[18] Zoetis T and Hurtt ME. Species comparison of anatomical and functional renal development. *Birth Defects Res. (Pt B)*. 2003;68:111-120.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[19], which would usually seem reasonable, given the findings in the embryofetal development studies. However, members of this pharmacological class are known to cause irreversible damage to the developing kidney of rats (kidney development occurs postnatally in rats and in utero in humans) (dapagliflozin AusPAR). Therefore, consistent with others in the pharmacological class, Pregnancy Category D[20] is considered more appropriate.

Local tolerance

Local tolerance of empagliflozin was studied in the form of topical dermal or eye irritation in rabbits and dermal sensitization was tested in mice. Studies were adequately conducted, all tests gave negative results.

Impurities

The proposed limits for three impurities in the drug substance have been toxicologically qualified.

Paediatric use

No juvenile animal studies were submitted. The sponsor claims that a juvenile rat study is planned. This study should be submitted for evaluation to the TGA as soon as it is available.

Nonclinical summary

- 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).
- In vitro, empagliflozin inhibited mouse, rat and human SGLT2 with nanomolar potency. In vivo, empagliflozin improved glucose tolerance in diabetic and obese animals and increased urinary glucose secretion at doses similar to the proposed clinical dose thus supporting the proposed dose and the proposed monotherapy indication.
- Combinations of empagliflozin with other antidiabetic agents (metformin, exenatide, insulin, pioglitazone, glipizide, linagliptin and voglibose) generally showed an additive (or almost additive) effect in blood glucose lowering in diabetic rats, thus supporting possible combination therapy.
- Empagliflozin showed high selectivity for SGLT2 over SGLT1 (human variants), the transporter responsible for glucose absorption in the gastrointestinal tract. There was no clinically relevant inhibition of other sugar transporters (human GLUT1, SGLT4, SGLT5, SGLT6) or other unrelated receptors, ion channels and different enzymes. No off-target activities are predicted at the proposed clinical dose.

[19] Category B3 for the use of medicines in pregnancy is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[20] Category D is defined as: *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. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

- CNS and respiratory function were unaffected in rats and no adverse effects on cardiovascular function were seen in a standard set of studies (effects on hERG K+ tail current, action potential duration in isolated guinea pig papillary muscles and ECG parameters in dogs). Safety margins are > 90 times the clinical Cmax. Increased gastric emptying was observed in rats (at 1.5 times the clinical Cmax). While this is considered clinically relevant it is not considered adverse. As expected by the mechanism of action empagliflozin treatment induced dose dependent increases in sodium, chloride and glucose measured in urine.
- The PK profile in mice, rats and dogs was considered sufficiently similar to that of humans to allow these species to serve as an appropriate model for the assessment of empagliflozin toxicity in humans.
- PK drug interactions involving CYP450 enzymes are unlikely. Inhibitors/inducers of OAT3, OATP1B1 and OATP1B3 could potentially alter the in vivo disposition of empagliflozin. In rats, no consistent PK interactions were evident with empagliflozin and metformin. Some interactions were seen with empagliflozin/linagliptin combinations, but these may not be clinically relevant.
- Empagliflozin showed a low order of acute toxicity by the oral route in rodents.
- Repeat dose toxicity studies were performed in mice, rats and dogs using the clinical route (PO) with very high relative exposures to empagliflozin achieved. In general, the toxicity profile of empagliflozin was similar to others in the pharmacological class with effects associated with the primary pharmacology of the drug (glucosuria, osmotic diuresis, effects on body weight and food consumption), secondary effects associated with SGLT2 inhibition (changes in the liver, pancreas and adrenals, other clinical chemistry changes and the risk of UTIs) or off-target effects on SGLT1 (gastrointestinal toxicity, effects on bone production and vascular mineralisation). The latter are not expected during clinical use.
- Additional findings not seen with others in the pharmacological class, included degenerative changes in the kidneys of male mice (single cell necrosis, tubular atrophy, tubular karyomegaly, tubular hypertrophy, cysts, cystic tubular hyperplasia and atypical tubular hyperplasia). A NOEL was not established for kidney damage in male mice. Mechanistic studies indicated these lesions were associated with metabolite(s) not present in humans. Exposures at the NOEL (for degenerative kidney lesions) in female mice, rats and dogs are reasonably high, ranging from 40 to 240 times the clinical AUC.
- Repeat dose toxicity studies of up to 13 weeks duration were conducted with empagliflozin/metformin and empagliflozin/linagliptin combinations to rats. No new or exacerbated toxicities were observed with the combination of empagliflozin and linagliptin. Additive or exacerbated effects with the combination (compared to either agent alone) included: effects on some RBC parameters (increased haematocrit), additive effects on lipid mobilisation and glycogen storage, hypochloraemia, depressed thymic weights and increased kidney weights. Exposures at the NOAEL were reasonable.
- Empagliflozin was not genotoxic in the standard battery of tests.
- No treatment related increase in tumour incidence was observed in female mice or female rats in approximately 2-year oral carcinogenicity studies. An increased incidence of renal atypical tubular hyperplasia, renal tubular adenomas and carcinomas was seen in male mice at doses resulting in exposures 45 times the clinical AUC. The underlying cause of these renal tumours appears to be associated with metabolite(s) not formed in humans. An increased incidence of haemangioma of the mesenteric lymph node was seen in male rats that received 700 mg/kg/day. Given the

reasonable safety margin, the tumours in rodents are considered to have low clinical relevance.

- High doses of empagliflozin did not affect male or female fertility in rats. Empagliflozin was shown to cross the placenta barrier only at very low levels and is excreted into milk. Adverse embryofetal effects in rats and rabbits were only seen at maternotoxic doses which resulted in high systemic exposures. Following maternal exposure, postnatal development in rats was impaired (decreased pup weight gain and transient deficits in learning and memory (males only)). Exposure at the NOEL was similar to the clinical AUC. As with others in the pharmacological class, empagliflozin should be considered to have a possible adverse effect on the developing kidney.

Conclusions and recommendation

- The primary pharmacology studies support the proposed monotherapy and combination therapy in adult patients with Type 2 diabetes.
- Empagliflozin should not be used during pregnancy or while breast-feeding.
- Findings in the toxicity studies of clinical relevance include:
  - Glucosuria, osmotic diuresis, effects on body weight
  - A risk for urinary tract infections
- Toxicity studies with empagliflozin/linagliptin indicate no additional concerns for the combination. Toxicity studies with empagliflozin/metformin indicated additive pharmacological effects.

There are no objections on nonclinical grounds to the registration of Jardiance for the proposed monotherapy indication and combination therapy with linagliptin or metformin. Support (in particular with regards to safety) for combinations of empagliflozin with all other possible glucose-lowering agents will need to rely solely on clinical data.

Recommended revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

IV. Clinical findings

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

Introduction

Empagliflozin is a novel, oral selective SGLT2 inhibitor. The proposed indication is: *as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.*

Clinical rationale

Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance and impaired insulin secretion. Diabetes is also associated with microvascular complications and elevated cardiovascular risk. The estimated worldwide prevalence of diabetes is 366 million with an increase of 50% expected within the next 20 years. The majority of these patients will be expected to have T2DM. The current treatment algorithm for T2DM involves lifestyle interventions such as diet and exercise, as well as the administration of oral or injectable antidiabetic drugs. Although initially effective, currently available oral

antidiabetic agents often fail to maintain long term glycaemic control or are associated with side effects that may limit their use. Hence, there is a need for new therapeutic options for patients with T2DM to provide sustained improvements in glycaemic control and to contribute in reducing cardiovascular risk factors such as increased body weight and hypertension.

The kidney has a role in the regulation of blood glucose levels and can therefore serve as a target for new antidiabetic drugs. SGLT2 is mainly expressed in the renal proximal tubules and accounts for approximately 90% of renal glucose re-absorption. Inhibition of SGLT2 decreases the renal re-absorption of glucose, thereby promoting glucose excretion in the urine resulting in reduction in blood glucose levels. Due to their insulin-independent mechanism of action, SGLT2 inhibitors have a low risk of hypoglycaemia. Further benefits of SGLT2 inhibition may include weight reduction due to the calorie loss associated with increased glucose excretion and a decrease in blood pressure (BP) that is possibly due to a mild diuretic effect.

Guidance

Regulatory guidelines for the development of diabetes drugs were followed in designing and adapting the clinical development programme for empagliflozin. These included:

- European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP): Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (draft) (20 January 2010, CPMP/EWP/1080/00 Rev. 1). 2010.
- EMA (CHMP): Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (14 May 2012, CPMP/EWP/1080/00 Rev.1). 2012.
- U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER): Guidance for industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention (draft guidance, February 2008). Rockville: 2008.
- US FDA. (CDER): Guidance for industry: diabetes mellitus - evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (December 2008). Silver Spring. 2008.

Contents of the clinical dossier

The clinical programme supporting this registration comprises of: 30 Phase I trials, 5 dose finding Phase II trials and 13 Phase IIb/III trials. A total of 11,250 randomised and treated patients are included in the evaluation of efficacy. Of these, 3021 patients were randomised to empagliflozin 10 mg and 3994 patients were randomised to empagliflozin 25 mg. Another 3081 patients were randomised to receive placebo and 1154 patients were randomised to an active comparator.

The submission contained the following clinical information:

- 30 clinical pharmacology studies;
- population PK analyses (U12-2525 and U12-2524);
- 4 pivotal efficacy/safety studies: monotherapy Trial 1245.20; add-on to metformin therapy (Trial 1245.23, met); add-on to metformin + sulfonylurea therapy (Trial

1245.23, metformin + sulfonylurea)[21]) and add-on to pioglitazone therapy ± metformin therapy (Trial 1245.19);

- 2 main dose finding Phase IIb studies (1245.9 and 1245.10);
- 6 additional studies are provided to support the long term efficacy and safety profile of empagliflozin in T2DM patients:
- Study 1245.33 (Add-on to basal insulin);
- Study 1245.36 (in T2DM patients with renal impairment);
- Study 1245.48 (in T2DM patients with hypertension and three ongoing studies (only interim reports up to 52 weeks) to support the long term efficacy and safety of empagliflozin in T2DM patients;
- Trial 1245.31: long term extension of the 4 pivotal studies ((Studies 1245.20, 1245.23(met), 1245.23 (metformin + sulfonylurea), 1245.19));
- Trial 1245.28: empagliflozin (25mg) compared with glimepiride (1mg to 4 mg) as add-on therapy to metformin over 52 and 104 weeks, with a further 104 week extension period;
- Trial 1245.25: large cardiovascular outcome trial (for up to 8 years) comparing empagliflozin with placebo in patients with high cardiovascular risk.
- Pooled analyses, meta-analyses, Integrated Summary of Efficacy, Integrated Summary of Safety
- Clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

Paediatric data

This submission did not include paediatric data.

Good clinical practice

All clinical trials followed the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), conformed to the Declaration of Helsinki and were conducted in accordance with Boehringer Ingelheim standard operating procedures. All clinical trial protocols were approved by institutional review boards or independent ethics committees. Written informed consent was obtained from all patients as per GCP requirement.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 below shows the studies relating to each PK topic.

[21] Trials 1245.23 (met) and 1245.23 (metformin + sulfonylurea) were conducted under a single trial number (1245.23), however for the purpose of data analyses, these trials were considered as 2 independent trials.

Table 4: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PKSingle dose Multi-dose	1245.1 1245.8 1245.5 None
	Bioequivalence † Single dose Multi-dose	1245.51 1275.3 1276.5 1276.9
	Food effect	1245.3 1245.79
PK in special populations	Target population § Single / multiple dosing Multi-dose PK-PD study	 1245.2 1245.4
	Hepatic impairment	1245.13
	Renal impairment	1245.12
	Neonates/infants/children/ adolescents	None
	Elderly	None
	Other special populations: PK-PD study in Chinese T2DM patients PK-PD study in Japanese T2DM patients	 1245.44 1245.15
Genetic/ gender related PK	Males versus females	None
	Other genetic variable	None
PK interactions	Metformin	1245.6
	Glimepiride	1245.7
	Pioglitazone	1245.17
	Warfarin	1245.18
	Sitagliptin	1245.27
	Linagliptin	1245.30
	Digoxin	1245.40

PK topic	Subtopic	Study ID
	Ethinylestradiol and levonorgestrel	1245.41
	Hydrochlorothiazide	1245.42
	Verapamil	1245.43
	Ramipril	1245.45
	Pioglitazone with various doses of B1 10773	1245.50
	Gemfibrozil	1245.58
	Simvastatin	1245.63
	Rifampicin and Probenecid	1245.83
Population PK analyses	Healthy subjects	None
	Target population	U12-2525-01

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

Evaluator's conclusions on pharmacokinetics

All the PK studies were well conducted, compliant with guidelines and used validated analytical methods. The PK of empagliflozin have been extensively characterised in healthy volunteers and patients with T2DM.

In healthy volunteers, empagliflozin showed linear PK characteristics following single oral doses over the dose range from 0.5 mg to 800 mg. Empagliflozin was rapidly absorbed reaching peak levels after a median time to reach Cmax (tmax) of 1 to 2 h. After reaching peak levels, plasma concentrations declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. The mean half life (t½) for doses 10 mg and above ranged from approximately 10 to 13 h. The proportion of drug excreted unchanged in urine over 72 h post-dose ranged from approximately 11 to 19% of dose. Renal clearance of empagliflozin ranged from 32 to 51 mL/min. Over the dose range studied, empagliflozin exposure ($AUC_{0-\infty}$ and Cmax) increased in a roughly dose proportional manner (Study 1245.1).

The PKs of empagliflozin were similar after a single dose and after multiple doses at steady state. After multiple oral dosing, empagliflozin reached steady state by Day 5. At steady state, peak levels were achieved at a median tmax of 1.5 h post-dose and, thereafter, plasma concentrations declined in a biphasic manner. The t½ of empagliflozin at steady state, after 4 weeks of treatment, was similar to that observed with single doses indicating linear PK with respect to time. The mean steady state t½ with 10 mg and 25 mg empagliflozin once daily (qd) was approximately 13 h. Consistent with t½, up to 22% drug accumulation, in terms of overall exposure (AUC), was observed at steady state. The proportion of unchanged parent compound excreted in urine at steady state was independent of the dose and averaged approximately 18% of dose. Renal clearance of

empagliflozin at steady state ranged from 36 to 37 mL/min. Empagliflozin exposure increased proportionally with an increase in dose over the dose range 2.5 to 100 mg after repeated dosing at steady state (Studies 1245.2 and 1245.4).

There were no clinically relevant differences in empagliflozin PK between healthy volunteers and patients with T2DM.

Absorption

After oral administration, empagliflozin was rapidly absorbed with a median tmax of 1.5 h post dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC was 4740 nmol.h/L and Cmax was 687 nmol/L with 25 mg empagliflozin qd. Systemic exposure of empagliflozin increased in a dose proportional manner. The single dose and steady state PK parameters of empagliflozin were similar suggesting linear PK with respect to time. Administration of 25 mg empagliflozin after intake of a high fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin PK was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

The apparent steady state volume of distribution was estimated to be 73.8 L, based on a population PK analysis. Following administration of an oral ^{14}C-empagliflozin solution to healthy subjects, the RBC partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug related material. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population PK analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With qd dosing, steady state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady state. Following administration of an oral ^{14}C-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Dose proportionality

Empagliflozin exposure increased in a roughly dose proportional manner over the dose range 0.5 mg to 800 mg following single oral administration in healthy volunteers (Trial 1245.1). Paired comparisons of dose groups indicated that increases in Cmax were dose proportional from 0.5 to 400 mg and slightly less than dose proportional from 400 to 800 mg. The PK characteristics of empagliflozin were similar after multiple dosing at steady state compared to single dose suggesting that empagliflozin demonstrates linear PK (Trial 1245.2). Consistent with these findings, increases in empagliflozin exposure were proportional to dose at steady state.

Bioequivalence between clinical trial and final marketing formulation

All 3 formulations used in the empagliflozin clinical development program had the same qualitative composition. TF-I and TF-II were uncoated tablets, and FF is a film coated tablet with a hypromellose based standard film coat. In vitro dissolution profiles depict immediate release characteristics and were similar for TF-II) and FF. Bioequivalence between the proposed commercial formulation and the TF-II formulation used in earlier clinical trials was demonstrated unequivocally. The 90% confidence intervals for the geometric mean ratios of both $AUC_{0-\infty}$ and Cmax were within the standard bioequivalence criteria of 80% to 125%.

PKs in special patient populations

The PKs of empagliflozin has not been evaluated in the paediatric population. Based on population PK analysis, there were no changes in empagliflozin PKs in elderly patients; gender, race, body mass index (BMI) also did not have any clinically relevant effect on empagliflozin PKs.

In patients with mild (estimated glomerular filtration rate (eGFR): < 90 mL/min/1.73 m^2), moderate (eGFR: < 60 mL/min/1.73 m^2), severe (eGFR: < 30 mL/min/1.73 m^2) renal impairment and patients with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to patients with normal renal function (eGFR: > 90 mL/min/1.73 m^2). Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Plasma Cmax of empagliflozin was roughly 20% higher in subjects with mild and severe renal impairment as compared to patients with normal renal function. In line with the Phase I Study 1245.12, the population PK analysis showed that the apparent oral clearance of empagliflozin decreased significantly with a decrease in eGFR leading to an increase in drug exposure. The changes in AUC at steady state ($AUC_{\tau,ss}$) were +18.5%, +49.2%, and +88.1% for patients with eGFR of 60, 30, and 15 mL/min/1.73 m^2, respectively, compared to a patients with a eGFR of 100 mL/min/1.73 m^2. The changes are not considered clinically relevant and, based on PK, no dosage adjustment is recommended in patients with renal insufficiency. However, because of the lack of efficacy in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), empagliflozin is not recommended for these patients (Study 1245.36).

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification[22], AUC of empagliflozin increased approximately by 23%, 47%, and 75% and Cmax by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. The population PK analysis showed that elevations of liver enzyme levels (AST, ALT, ALP, and lactate dehydrogenase (LDH)) had no statistically significant impact on the apparent oral clearance of empagliflozin. The observed changes in empagliflozin exposure are not considered clinically relevant and, based on PK, no dosage adjustment is recommended in patients with hepatic impairment.

Drug interactions

Empagliflozin PK characteristics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, verapamil, ramipril, hydrochlorothiazide, and torasemide. Empagliflozin exposure (AUC) increased by 1.59 fold following co-administration with gemfibrozil, 1.35 fold with

[22] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease (encephalopathy, ascites, serum bilirubin, serum albumin and prothrombin time). Each measure is scored 1-3, with 3 indicating most severe derangement. Assessment as good operative risk (A or mild) if 5 or 6 points; moderate risk (B or moderate) if 7 to 9 points; and poor operative risk (C or severe) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics.).

rifampicin, and 1.53 fold with probenecid. The observed increases in the overall exposure of empagliflozin were not considered to be clinically relevant and no dosage adjustment of empagliflozin is recommended when administered concomitantly with gemfibrozil, rifampicin, or probenecid. Empagliflozin had no clinically relevant effect on the PK of metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torasemide, and oral contraceptives when co-administered.

The effects of smoking, diet, herbal products, and alcohol use on the PK of empagliflozin have not been specifically studied. This issue was subsequently addressed by the sponsor in response to TGA questions.

Two studies (1245.17 and 1245.50) investigated PK drug interactions between empagliflozin and pioglitazone (and its active metabolites) and showed contrasting results. Due to inconsistent results across the 2 studies, it would be prudent to exercise caution during co-administration of empagliflozin with pioglitazone in treatment of T2DM. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. While a causal relationship between empagliflozin and bladder cancer is unlikely (see Adverse effects), as a precautionary measure, empagliflozin should not be recommended for use in patients concomitantly treated with pioglitazone (similar to PI for dapagliflozin). This issue was subsequently addressed by the sponsor in response to the Delegate's Overview (see below).

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

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 below shows the studies relating to PD.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	PK-PD study effect on urinary glucose excretion and glucose control	1254.2 1254.4
Secondary Pharmacology	Effect on QT interval	1245.16
Gender other genetic and Age-Related Differences in PD Response	Effect of race- in Japanese subjects	1245.15
	Effect of age	None
	Effect of gender	None
	Effect of genetic characteristic	None
PD Interactions	Hydrochlorothiazide or toresemide	1245.42

PD Topic	Subtopic	Study ID
Population PD and PK-PD analyses	Healthy subjects	None
	Target population	U12-2524, U12-2525

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

Evaluator's conclusions on pharmacodynamics

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000 fold selectivity over human SGLT1 (IC_{50} of 6278 nM), responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with T2DM and hyperglycaemia a higher amount of glucose is filtered and reabsorbed. Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose re-absorption. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

Oral administration of empagliflozin resulted in a dose dependent increase in UGE. In healthy volunteers (Study 1245.2), UGE was higher with all doses (0.5 mg to 800 mg) compared with placebo. Following a single oral administration of empagliflozin, up to 91 g of glucose was excreted in urine. Empagliflozin inhibited reabsorption of < 40% of filtered glucose with single daily doses up to 10 mg and approximately 40 to 60% of filtered glucose at higher doses, with the effect reaching a plateau at around the 100 mg dose. At doses less than 50 mg, the majority of glucose was excreted in the first 24 h, but at doses of 100 mg and above, glucose excretion continued for up to 48 to 72 h. The time to reach the maximum rate of UGE was 7 h in most subjects and was similar in all dose groups.

Empagliflozin administration resulted in increased UGE in patients with T2DM (Study 1245.4). Empagliflozin inhibited reabsorption of 39%, 46%, 58%, and 64% of filtered glucose with 2.5, 10, 25, and 100 mg qd doses, respectively. Consistent with the extent of inhibition of glucose reabsorption, UGE seemed to plateau after the 10 mg dose, with total cumulative amounts excreted ranging from 77.9 g to 89.8 g with 10 to 100 mg empagliflozin after a single dose. Increased UGE was maintained over the 8 day treatment duration and 4 week treatment, and similar results were observed after multiple doses with or without oral glucose tolerance test (OGTT). Following a 4 week treatment in patients, increases in UGE from baseline were approximately 64.4 g, 78.4 g and 72.6 g with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively. Increased UGE with empagliflozin treatment did not result in clinically relevant changes in urine volume.

Following a 4 week treatment in Japanese patients with T2DM (Study 1245.15), adjusted mean changes from baseline in UGE increased with empagliflozin dose; 40.8 g, 77.1 g, 80.9 g, 93.0 g and -2.1 g for the 1 mg, 5 mg, 10 mg, 25 mg empagliflozin and placebo groups, respectively. Following 8 day treatment in Chinese patients, the amounts of UGE were similar with 10 mg and 25 mg empagliflozin qd; 95.8 g and 82.6 g, respectively. The increase in UGE was maintained with multiple dosing.

As expected, increased glucosuria did not have any effect on plasma glucose levels in healthy volunteers. In patients with T2DM, all empagliflozin dose groups showed reductions in plasma glucose compared to placebo. Declines in fasting plasma glucose (FPG) were observed immediately after the first dose of empagliflozin and were

maintained over the entire treatment duration. After 4 week treatment, FPG decreased by approximately 44 mg/dL, 34 mg/dL and 29 mg/dL with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively, compared to 4 mg/dL with placebo. In addition, mean daily plasma glucose (MDG) levels, determined using 8 point plasma glucose profiles, decreased by approximately 20 mg/dL, 26 mg/dL, and 24 mg/dL with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively, compared to 5 mg/dL with placebo.

Overall, in patients with T2DM, UGE increased immediately following the first dose of empagliflozin and is continuous over the 24 h dosing interval. Increased UGE was maintained at the end of 4 week treatment period, averaging approximately 78 g/day with 25 mg empagliflozin qd. Increased UGE resulted in an immediate reduction in plasma glucose levels in patients with T2DM. Empagliflozin improves both fasting and post-prandial plasma glucose levels. The insulin independent mechanism of action of empagliflozin contributes to a low risk of hypoglycaemia.

The 5 period crossover trial (1245.16) in 30 healthy male and female subjects demonstrated that single oral doses of 25 mg empagliflozin (expected therapeutic dose) and 200 mg empagliflozin (supratherapeutic dose) were not associated with a QT(c) interval prolongation.

In population PK-PD analysis U12-2525, FPG and HbA1c responses were described as being dependent on drug exposure. The maximal effect (20% lowering of FPG) achieved by empagliflozin treatment was increased with increasing baseline FPG. The maximal effect is attenuated with decreased eGFR despite an increase in empagliflozin exposure, but was still maintained to nearly half of the maximal effect with eGFR as low as 30mL/min/1.73m^2. The exposure response modelling estimated that targets of 80% and 90% of the maximal response after 24 weeks of treatment for FPG and HbA1c were obtained by oral empagliflozin qd doses of approximately 10 and 25 mg. Rates of the adverse event (AE)/tolerability endpoints tested (UTI, GB virus (GBV) infection, hypoglycaemia) did not increase significantly with increasing empagliflozin AUC_{ss}. GBV events occurred at a higher rate in patients taking active empagliflozin compared to those taking placebo. There was no discernible effect of empagliflozin exposure (AUC_{ss}) on eGFR change from baseline.

Dosage selection for the pivotal studies

Two studies were conducted:

- Phase IIb dose ranging Study 1245.9

Study 1245.9 was a Phase IIb, randomised, parallel group study to evaluate the safety, efficacy, and PK study of empagliflozin (5 mg, 10 mg and 25 mg) administered orally qd over 12 weeks compared double blind to placebo, as monotherapy, with an additional open label metformin arm in T2DM patients with insufficient glycemic control.

The main inclusion criteria were: Male and female patients, age ≥ 18 and < 80 years, with a diagnosis of T2DM, either treatment naïve (on no antidiabetic therapy for the 10 weeks prior to screening) or on a maximum of one oral antidiabetic therapy (except glitazones, glucagons-like peptide 1 analogues or insulin) on a stable dose for the 10 weeks prior to screening; HbA1c at screening for patients treated with one other oral antidiabetic drug: HbA1c ≥ 6.5 to ≤ 9.0% and for treatment naïve patients: HbA1c > 7.0 to ≤ 10.0%; HbA1c at Visit 2 (start of run-in) for all patients: HbA1c > 7.0 to ≤ 10.0%; BMI ≤ 40 kg/m^2.

- Phase II dose ranging Study 1245.10

Study 1245.10 was a Phase II, randomised, parallel group safety, efficacy, and PK study of empagliflozin (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) administered orally qd over 12

weeks compared double blind to placebo with an additional open label sitagliptin arm in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy.

The main inclusion criteria were male and female patients with a diagnosis of T2DM and previously treated with metformin alone or with metformin and one other oral antidiabetic drug (antidiabetic therapy has to be unchanged for at least 10 weeks prior to screening); Age ≥ 18 and < 80 years, stable metformin therapy ≥ 1500 mg/day for at least 10 weeks, BMI ≤ 40 kg/m^2; HbA1c at Visit 1A (Screening): for patients treated with metformin and one other oral antidiabetic drug: HbA1c ≥ 6.5% to ≤ 9.0%; for patients treated with metformin only: HbA1c > 7.0% to ≤ 10.0%; HbA1c at Visit 2 (start of Run-in) for all patients: HbA1c > 7.0 to ≤ 10.0%.

Evaluator's conclusion on dosage selection

Based on the analysis of the primary endpoint and some of the important secondary endpoints in the 2 dose-ranging studies, both 10 mg and 25 mg doses of empagliflozin were most efficacious in regard to HbA1c and FPG lowering with the 50 mg dose showing no further increase in efficacy; in fact, the 50 mg dose showed numerically lesser reductions in HbA1c and FPG compared with 10 and 25 mg doses while the 1 mg dose failed to show significant efficacy compared with placebo. All doses of empagliflozin were well tolerated. Hence, the selection of the 10 mg and 25 mg doses of empagliflozin for the pivotal Phase III studies appears to be appropriate.

Efficacy

Studies providing efficacy data

As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus

The main proof of efficacy is provided by four pivotal, double blind, placebo controlled Phase III trials in which empagliflozin was investigated as monotherapy (Study 1245.20) or as add-on therapy to oral antidiabetic background medication (Studies 1245.19 and 1245.23). Study 1245.23 comprised two separate trials (based on the type of oral antidiabetic background medication) under a single trial number: 1245.23 (met) and 1245.23 (metformin + sulfonylurea). The four extensions of the pivotal trials were conducted under one trial number (1245.31) and provided data to support the persistence of efficacy of empagliflozin up to 52 weeks.

Further evidence of efficacy is provided by five additional double blind studies conducted in patients with diabetes: an active controlled trial comparing empagliflozin with glimepiride (1245.28), a trial including patients taking basal insulin as background therapy (1245.33), and trials including patients with hypertension (1245.48), increased cardiovascular risk (1245.25) and renal impairment (1245.36). With the exception of the 12 week Trial 1245.48, all of these trials include long term analyses of efficacy data over at least 52 weeks. Additional evidence of the persistence efficacy over 90 weeks is provided by a combined analysis of two dose finding trials (1245.9 and 1245.10) and their open label extension trial (1245.24).

Evaluator's conclusions on efficacy

Regulatory guidelines[23] for the development of diabetes drugs were followed in designing and adapting the clinical development programme for empagliflozin. Overall, 13767 subjects were included and treated in the clinical trials constituting the development programme presented in this application. A total of 8506 patients with T2DM were treated with empagliflozin (empagliflozin 25 mg: 4563 patients, empagliflozin 10 mg: 3311 patients). Of these, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. The clinical programme exceeds the requirements of relevant guidelines and provides adequate and sufficient information for the assessment of efficacy empagliflozin as treatment for type 2 diabetes in adults. Patient population studied was representative of the target patient population in which empagliflozin is proposed to be used.

Treatment with empagliflozin 10 mg or 25 mg qd resulted in a robust improvement of glycaemic control with statistically significant and clinically meaningful reductions of HbA1c and FPG. The 4 pivotal trials demonstrated the superiority of both doses of empagliflozin to placebo after 24 weeks. In 3 of the 4 trials, the effects for the 25 mg dose were numerically larger than for the 10 mg dose. The effects were consistent across a range of different antidiabetic background regimens. Thus, empagliflozin improved glycaemic control as monotherapy and as add-on to metformin monotherapy, metformin plus sulfonylurea, and pioglitazone (with or without metformin). Almost maximal efficacy of empagliflozin on glycaemic control was established already 12 weeks after the start of treatment. Efficacy was sustained for at least 52 weeks, as shown in the double blind extensions of the 4 pivotal trials. The proportions of patients reaching the target HbA1c (< 7.0%) at week 24 were significantly larger for both empagliflozin doses than for placebo in each trial; treatment with empagliflozin 25 mg led to higher responder rates than treatment with empagliflozin 10 mg. In addition, significantly fewer patients in the empagliflozin groups required rescue medication than patients in the placebo groups. The results for HbA1c and FPG were further supported by reductions in mean daily glucose and postprandial glucose, which were investigated in two of the pivotal trials.

Empagliflozin also provided significant and clinically meaningful reductions in HbA1c compared with placebo in all other Phase III placebo controlled trials, that is, in patients treated with basal insulin, in patients with type 2 diabetes and hypertension, in patients with mild and moderate renal impairment, and in patients with increased cardiovascular risk (including a subpopulation of patients with increased cardiovascular risk on a background of metformin and DPP-4 inhibitor, with or without one additional oral antidiabetic agent).

The HbA1c-lowering effect of empagliflozin was generally consistent across various subgroups based on demographic factors or baseline characteristics. These were gender, race (White, Asian, Black), ethnicity, geographical region, BMI, time since diagnosis of diabetes, and extent of insulin resistance (Homeostasis Model Assessment index to assess Insulin Resistance; HOMA-IR) and insulin secretion (Homeostasis Model Assessment index to assess Insulin Secretion; HOMA-IS). Higher baseline HbA1c values were associated with greater empagliflozin mediated reductions in HbA1c. There is a high prevalence of chronic kidney disease in patients with type 2 diabetes, and only limited treatment options for patients with impaired renal function are available due to safety and tolerability concerns.

[23] These included EMA's draft "Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus" (20 January 2010, CPMP/EWP/1080/00 Rev. 1) 2010; EMA's final "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (14 May 2012, CPMP/EWP/1080/00 Rev. 1) 2012; FDA's "Draft Guidance for Industry – Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention" (February 2008, Rockville) 2008; and FDA's "Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (December 2008, Silver Spring) 2008.

As expected, given the mechanism of action of empagliflozin, a gradual reduction in efficacy of empagliflozin was observed with increasing degree of renal impairment. However, empagliflozin provided statistically significant and clinically meaningful reductions in HbA1c even in patients with moderate renal impairment (in a trial in patients with type 2 diabetes and renal impairment). Relevant reductions of HbA1c were achieved in both, patients with chronic kidney disease Stage 3A (moderate renal impairment A; eGFR 45 to <60 mL/min/1.73 m^2) and patients with chronic kidney disease Stage 3B (moderate renal impairment B; eGFR 30 to <45 mL/min/1.73 m^2). Reduced efficacy of empagliflozin was seen with increasing age but HbA1c improvements compared with placebo were clinically meaningful in all subcategories of patients younger than 75 years. It was the opinion of the evaluator that the reduced efficacy in patients aged 75 years or older appeared to be largely driven by the generally decreased renal function in these patients.

Body weight reduction and optimum control of BP are two important unmet needs in the management of patients with type 2 diabetes. Empagliflozin treatment led to statistically significant and clinically meaningful reductions in body weight in all pivotal trials. Furthermore, significant and clinically meaningful reductions of systolic BP (SBP) compared with placebo were achieved for empagliflozin 25 mg in each of the pivotal trials. For diastolic BP (DBP), reductions were also observed but were smaller and not always significant compared with placebo. In an ambulatory BP monitoring (ABPM) trial in patients with type 2 diabetes and hypertension, both doses of empagliflozin were superior to placebo in reducing 24 h SBP and 24 h DBP after 12 weeks of treatment. Weight and BP reductions of a magnitude similar to that in the pivotal trials were reached in the other supportive trials including the trials in patients with renal impairment or with high cardiovascular risk. Notably, in patients without hypertension, treatment with empagliflozin was not associated with an increased frequency of AEs indicative of hypotension. The weight and BP reductions were sustained throughout the short- and long-term trials. The effects of empagliflozin on body weight and BP are expected to modify cardiovascular risk factors and cardiovascular risk, and may translate into a benefit on the long-term micro- and macro-vascular complications of diabetes that extend beyond the effect on glycaemic control. However effect of empagliflozin on morbidity and mortality has not yet been established.

Empagliflozin 25 mg was compared to the established antidiabetic drug glimepiride. In this double blind trial (1245.28), empagliflozin was shown to provide non-inferior glycaemic control to glimepiride (up to 4 mg daily) after 52 weeks of treatment. At the same time, empagliflozin was superior to glimepiride for several other clinically important endpoints, namely body weight reduction, a reduced occurrence of confirmed hypoglycaemic events, and for SBP and DBP reductions. Thus, similar glycaemic control was complemented by added benefits of empagliflozin 25 mg compared with glimepiride.

Metformin is the current standard first line treatment for patients with type 2 diabetes. New antidiabetic drugs will therefore likely be employed as combination therapy, for example, with metformin, or as monotherapy in patients for whom metformin is inappropriate. Sitagliptin is one of the few antidiabetic drugs with such a restricted monotherapy claim (in the EU). Therefore, empagliflozin (25 mg) efficacy was compared with that of sitagliptin (100 mg) in the pivotal monotherapy trial (1245.20) and its extension. For most endpoints, the exploratory comparison of both empagliflozin doses versus sitagliptin provided a larger treatment effect of empagliflozin. Treatment with empagliflozin 25 mg showed a numerically greater reduction in HbA1c than treatment with sitagliptin; the reduction in HbA1c for treatment with empagliflozin 10 mg was almost identical to that for sitagliptin. Treatment with both empagliflozin 10 mg and 25 mg reduced body weight and BP compared with sitagliptin treatment, although there was no direct statistical comparison between empagliflozin and sitagliptin. The usefulness of

empagliflozin in the monotherapy setting was further substantiated in a 12 week, double blind, placebo controlled Phase IIb trial with an open label (immediate release) metformin group. Long term data of up to 90 weeks from the open label extension of this trial showed sustained and similar improvements of glycaemic control with empagliflozin 25 mg and with metformin. These results suggest that empagliflozin may be an effective treatment option in patients for whom metformin is considered inappropriate. In this context, the added benefits of empagliflozin compared with the sulfonylurea glimepiride, which is also an alternative when metformin is inappropriate, are even more important.

In most of the trials, the 25 mg dose of empagliflozin showed better efficacy than the 10 mg dose. This was true for all endpoints (HbA1c, FPG, body weight, SBP, DBP). A higher proportion of patients reached the HbA1c target of < 7% with empagliflozin 25 mg than with empagliflozin 10 mg. Fewer patients treated with the high empagliflozin dose required rescue medication than patients treated with the low empagliflozin dose.

Long term efficacy

In the Phase III, double blind extension Study 1245.31 (extension of the four 24 week pivotal studies for another 52 weeks), treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful improvement of glucose control, weight, and BP in patients with T2DM who were either drug naïve or on a background treatment with pioglitazone, metformin alone, or metformin and sulfonylurea, which was sustained over 52 weeks of treatment. For HbA1c, mean changes relative to placebo after 52 weeks across the studies were statistically significant and ranged from -0.54 to -0.76% in the empagliflozin 10 mg group and from -0.63 to -0.91% in the empagliflozin 25 mg group. In drug naïve patients, both doses showed a numerically larger decrease in mean HbA1c compared with sitagliptin (empagliflozin 10 mg: -0.10%; empagliflozin 25 mg: -0.25%). In all studies, mean HbA1c levels decreased in both empagliflozin groups for up to 24 weeks and then remained stable until week 52, while little change from baseline was seen for placebo patients. An important treatment target for patients with type 2 diabetes is adequate glycaemic control, which is defined as HbA1c < 7.0% according to the American Diabetes Association and the European Association for the Study of Diabetes. In all 4 studies, the incidences of patients with glycaemic control were higher for the empagliflozin doses than for placebo, with exploratory odds ratios of empagliflozin over placebo ranging from 2.215 to 5.828 across the studies, and with empagliflozin 25 mg consistently showing the highest percent treatment response. These results are supported by a reduction in FPG sustained up to week 52 in all studies. In addition, use of antidiabetic rescue medication was less common for the empagliflozin treatments than for placebo (all studies) and sitagliptin (drug naïve). In summary, both empagliflozin doses led to a clinically meaningful and durable improvement of glycaemic control in patients who were drug naïve or received either: pioglitazone, metformin, or metformin/sulfonylurea as background therapy.

For body weight, mean changes relative to placebo after 52 weeks across the studies were statistically significant and ranged from -1.58 to -2.07 kg in the empagliflozin 10 mg group and from -1.83 to -2.19 kg in the empagliflozin 25 mg group. The treatment effect in comparison with sitagliptin in drug naïve patients was even more pronounced (empagliflozin 10 mg versus sitagliptin: -2.21 kg; empagliflozin 25 mg versus sitagliptin: -2.77 kg). Mean body weight in both empagliflozin groups decreased for up to 24 weeks and was then sustained until week 52 in all studies. Of note, the reduction in body weight with empagliflozin was less pronounced in patients with baseline HbA1c ≥ 8.5% than in those with baseline HbA1c < 8.5% across studies. This is consistent with the observation that patients with poor glycaemic control, who tend to be in a catabolic state, are likely to gain weight when their glucose metabolism improves. Numerically more patients receiving empagliflozin (up to 20.3%) than receiving placebo (up to 6.8%) showed a > 5% reduction in body weight after 52 weeks across the studies (and also when

compared with sitagliptin treatment in drug naïve patients). These findings were supported by a sustained reduction in waist circumference relative to placebo in both empagliflozin groups across studies. For BP, the mean changes relative to placebo in SBP at week 52 were statistically significant and ranged from -2.8 to -4.6 mmHg in the empagliflozin 10 mg group and from -2.9 to -4.8 mmHg in the empagliflozin 25 mg group. In drug naïve patients, a significant decrease in mean SBP relative to sitagliptin was seen (empagliflozin 10 mg versus sitagliptin: -2.7 mmHg; empagliflozin 25 mg versus sitagliptin: -2.6 mmHg). These findings were supported by reductions in DBP relative to placebo in both empagliflozin groups across studies, albeit an only slight reduction seen for patients receiving metformin/sulfonylurea.

When evaluating the combined benefits of empagliflozin (glucose control, reduced weight and BP) as a composite endpoint, it was found that more patients treated with either empagliflozin dose than treated with placebo (all studies) or sitagliptin (drug naïve) achieved a combined reduction in HbA1c by at least 0.5%, body weight by > 2%, and SBP by > 3 mmHg. Both empagliflozin groups showed changes in biomarkers for insulin resistance and secretion (assessed in 3 studies: drug naïve, metformin, and metformin/sulfonylurea) that consistently suggest an improvement in beta cell function and insulin resistance.

Limitations of data submitted and comments on proposed Indication

The *Indication* section of the proposed PI should specify the uses of empagliflozin as monotherapy and combination therapy. Patients on GLP-1 analogues were also excluded from all pivotal clinical trials.

Safety

Studies providing safety data

Overall, 48 studies provided evaluable safety data for empagliflozin. For safety analyses, the studies were pooled into 6 groupings (Safety trial pooling (SAFs) 1 to 6) (Table 6 below).

Table 6: Study groupings for integrated safety analyses

Study grouping	Description	Studies included
SAF-1	Studies with empagliflozin monotherapy (in patients without background antidiabetic therapy)	Phase II: 1245.9, 1245.38 (only until 12 weeks) Phase III: 1245.20, 1245.31 monotherapy (only patients from 1245.20)
SAF-2 (= EFF-1)	Pivotal studies, excluding patients receiving an SU as background therapy	Phase III: 1245.19, 1245.20, 1245.23$_{(met)}$
SAF-3 (= EFF-2)	Pivotal studies and their extension, including all patients	Phase III: 1245.19, 1245.20, 1245.23$_{(met)}$, 1245.23$_{(met+SU)}$, 1245.31
SAF-4	All studies in patients with type 2 diabetes and without special medical conditions (renal impairment or increased cardiovascular risk)	Phase I: 1245.2, 1245.4, 1245.44 Phase II: 1245.9, 1245.10, 1245.15, 1245.24, 1245.33, 1245.38 Phase III:1245.19, 1245.20, 1245.23$_{(met)}$, 1245.23$_{(met+SU)}$, 1245.28, 1245.31, 1245.48
SAF-5	All studies in patients with type 2 diabetes[1]	Phase I: 1245.2, 1245.4, 1245.44 Phase II: 1245.9, 1245.10, 1245.15, 1245.24, 1245.33, 1245.38 Phase III:1245.19, 1245.20, 1245.23$_{(met)}$, 1245.23$_{(met+SU)}$, 1245.25, 1245.28, 1245.31, 1245.36, 1245.48
SAF-6	All studies in healthy subjects[2]	Phase I: 1245.1, 1245.3, 1245.5, 1245.6, 1245.7, 1245.8, 1245.16, 1245.17, 1245.18, 1245.27, 1245.30, 1245.40, 1245.41, 1245.43, 1245.45, 1245.50, 1245.51, 1245.58, 1245.63, 1245.79, 1275.3, 1275.5, 1276.9

Separate safety analyses were performed for Study 1245.25 and cardiovascular safety meta-analysis report (U12-2463). 1: Not including Study 1245.42 (drug interaction with diuretics in patients with T2DM) because it was a crossover design. 2: Not including Study 1245.83 because it was completed too late to be included.

SAF-1 pool was used for the safety assessment of empagliflozin administered as monotherapy. As the largest pool of patients, SAF-5 was used for safety subgroup analyses.

Patient exposure

A total of 13183 patients with type 2 diabetes were treated in the clinical studies; of these, 3311 patients were treated with empagliflozin 10 mg, 4563 were treated with empagliflozin 25 mg, and 4697 were treated with comparator medications (placebo, metformin, sitagliptin and glimepiride). The number of treated subjects in all clinical studies are summarised in Table 7 and the numbers of treated subjects in all safety groupings and Study 1245.25 are summarised in Table 8.

Table 7: Number of treated subjects in clinical studies

Phase	Objective	BI Trial No.	Empa 10	Empa 25	All empa	All other treatments	Total
I		1245.1	6	6	52	18	70
		1245.3	0	0	14	0	14
		1245.8	0	0	8	0	8
	Pharmacokinetic and pharmacodynamic studies in healthy subjects	1245.16	0	28	30	29	30
		1245.51	0	24	24	0	24
		1245.79	18	18	18	0	18
		1275.3	0	41	42	0	42
		1276.5	0	0	16	0	16
		1276.9	16	0	16	0	16
	Studies in subjects with type 2 diabetes	1245.2	9	9	36	12	48
		1245.4	16	16	62	16	78
	Studies in special populations	1245.5	12	6	36	12	48
		1245.12	0	0	40[1]	0	40[1]
		1245.13	0	0	36[2]	0	36[2]
		1245.44	9	9	18	6	24
	Drug-drug interaction studies	1245.6	0	0	16	16	16
		1245.7	0	0	16	16	16
		1245.17	0	0	19	20	20
		1245.18	0	18	18	18	18
		1245.27	0	0	16	16	16
		1245.30	0	0	16	16	16
		1245.40	0	20	20	20	20
		1245.41	0	18	18	18	18
		1245.42	0	21	21	21	22
		1245.43	0	16	16	16	16
		1245.45	0	23	23	23	23
		1245.50	18	17	16	20	20
		1245.58	0	18	18	18	18
		1245.63	0	18	18	17	18
		1245.83	18	0	18	18	18
II	Dose-finding studies and extensions	1245.9	81	82	244	162	406
		1245.10	71	70	353	142	495
		1245.24	272	275	547	112	659
		1245.15	20	19	79	21	100
		1245.38	109	109	438	109	547
	With basal insulin therapy	1245.33	169	155	324	170	494
III	24-week pivotal studies	1245.19	165	168	333	165	498
		1245.20	224	310[3]	534[3]	452	986[3]
		1245.23 *(met)*	217	283[3]	500[3]	206	706[3]
		1245.23 *(met+SU)*	224	318[3]	542[3]	225	767[3]
	Other phase III studies	1245.25	1623	1632	3255	1619	4874
		1245.28	0	765	765	780	1545
		1245.31	607	582	1189	667	1856
		1245.36	98	321	419	319	738
		1245.48	276	276	552	272	824
Total[4]	patients with type 2 diabetes		3311	4563	8506	4697	13183
	patients and healthy subjects		3399	4834	9055	5008	13767

[1] In study 1245.12, 28 of the 40 subjects had type 2 diabetes
[2] In study 1245.13, 3 of the 36 subjects had type 2 diabetes
[3] Including patients assigned to the open-label empagliflozin 25 mg arm in 1245.20, 1245.23 *(met)*, and 1245.23 *(met+SU)*
[4] Patients in extension studies (1245.24 and 1245.31), who were the same as in the preceding studies, were not counted in the total

Table 8: Number of treated subjects in safety groupings

Grouping Study	Placebo	Empa <10 mg	Empa 10 mg	Empa 25 mg	Empa >25 mg	All (randomised) empa	All comparators[1]	Total randomised[2]	Open-label empa 25 mg
SAF-1	420	191	414	414	110	1129	723	1852	87
1245.9	82	81	81	82	--	244	162	406	--
1245.20	229	--	224	223	--	447	452	899	87
1245.31[3]	136[3]	--	165[3]	159[3]	--	324[3]	291[3]	615[3]	--
1245.38	109	110	109	109	110	438	109	547	--
SAF-2	600	--	606	605	--	1211	823	2034	156
1245.19	165	--	165	168	--	333	165	498	--
1245.20	229	--	224	223	--	447	452	899	87
1245.23*(met)*	206	--	217	214	--	431	206	637	69
SAF-3	825	--	830	822	--	1652	1048	2700	257
1245.19	165	--	165	168	--	333	165	498	--
1245.20	229	--	224	223	--	447	452	899	87
1245.23*(met)*	206	--	217	214	--	431	206	637	69
1245.23*(met+SU)*	225	--	224	217	--	441	225	666	101
1245.31[3]	512[4]	--	607[4]	582[4]	--	1189	667	1856[4]	--
SAF-4	1584	382	1590	2332	219	4523	2738	7261	--
SAF-5	3522	382	3311	4285	219	8197	4676	12873	--
SAF-6	59	24	52	194	169	393[5]	246[6]	521	--
1245.25	1619	--	1623	1632	--	3255	1619	4874	--

[1] Including all active comparators and placebo except for SAF-6. For SAF-1 all comparators includes placebo, metformin, and sitagliptin; for SAF-2 and SAF-3 all comparators includes placebo and sitagliptin; for SAF-4 and SAF-5 all comparators includes placebo, metformin, sitagliptin, and glimepiride; for 1245.25 all comparators corresponds to placebo.
[2] Only randomised patients, not including open-label empagliflozin 25 mg
[3] Only patients who had completed the preceding study 1245.20; these patients had no background antidiabetic medication
[4] Patients could only enter the extension study 1245.31 if they completed one of the preceding studies (1245.19, 1245.20, 1245.23*(met)*, and 1245.23*(met+SU)*)
[5] Subjects treated with empagliflozin alone in at least 1 treatment period; some of these subjects were co-administered empagliflozin and other active drugs in other treatment periods in the same study
[6] Subjects treated with any active comparator drug alone in at least 1 treatment period; some of these subjects were co-administered empagliflozin and other active drugs in other treatment periods in the same study

Safety issues with the potential for major regulatory impact

Liver toxicity

The incidence of elevated ALT/AST was low and similar in empagliflozin and comparator groups. Furthermore, there were no reports of Hy's law[24] cases in the large database of subjects treated with empagliflozin.

Haematological toxicity

Empagliflozin treatment slightly increased haematocrit values (absolute change from baseline around 3%), but the increase in haematocrit was reversible after the discontinuation of empagliflozin treatment; the frequencies of patients with thromboembolic AEs did not increase with empagliflozin treatment (0.08% for 10 mg and 0.09% for 25 mg; 0.23% for placebo).

Serious skin reactions

None.

Cardiovascular safety

In order to assess the cardiovascular risk of empagliflozin treatment compared with any control, a cardiovascular meta-analysis was planned. The primary endpoint was the composite 4 point major adverse cardiovascular events (MACE) endpoint, which consisted of cardiovascular death (including fatal stroke and fatal myocardial infarction), non-fatal myocardial infarction, non-fatal stroke and hospitalisation due to unstable angina.

The primary endpoint was the 4-point MACE composite endpoint. Time to first occurrence of any component was calculated, as based on adjudicated results.

- CV death (including fatal stroke and fatal myocardial infarction; MI);
- Non-fatal MI;
- Non-fatal stroke: ischaemic and haemorrhagic stroke;
- Hospitalisation due to unstable angina.

The cardiovascular risk ratio of empagliflozin treatment (the 2 test doses combined) against control treatment (all control treatments combined) and the associated confidence interval (CI) were calculated. The overall significance level for the meta-analysis was $\alpha = 2.5\%$, one-sided. An interim analysis was planned and an α-spending approach was used to compensate for the repeated testing.

Secondary endpoints were the 3-point MACE[25], 5-point MACE[26], and 7-point MACE[27] composite endpoints. For each, time to first occurrence of any component was calculated (based on adjudicated results). Tertiary endpoints were the time to first occurrence of

[24] Briefly, Hy's Law cases have the following three components: 1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3 fold or greater elevations above the upper limit of normal (ULN) of ALT or AST than the (non-hepatotoxic) control drug or placebo 2. Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum total bilirubin (TBL) to >2xULN, without initial findings of cholestasis (elevated serum ALP) 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.
[25] Three-point MACE:CV death (including fatal stroke and fatal MI); Non-fatal MI; Non-fatal stroke: ischaemic and haemorrhagic stroke.
[26] Five-point MACE: CV death (including fatal stroke and fatal MI); Non-fatal MI; Non-fatal stroke: ischaemic and haemorrhagic stroke; Hospitalisation due to unstable angina; Hospitalisation due to congestive heart failure.
[27] Seven-point MACE: CV death (including fatal stroke and fatal MI); Non-fatal MI; Non-fatal stroke: ischaemic and haemorrhagic stroke; Hospitalisation for unstable angina; Hospitalisation due to congestive heart failure; Transient ischaemic attack (TIA); Coronary revascularisation procedures.

each individual component of the 7-point MACE endpoint and of all-cause mortality. Additional endpoints were time to first MI (fatal and non-fatal) and stroke (fatal and nonfatal).

Unwanted immunological events

None.

Postmarketing data

No post-marketing data are available.

Evaluator's conclusions on safety

To support an integrated analysis of safety, the trial data were pooled to adequately analyse the different aspects of the safety profile of empagliflozin. The most relevant safety pooling for the benefit-risk assessment of empagliflozin is SAF-3 (pool of pivotal trials with extensions, 2957 patients in total) as this pooling corresponds to the efficacy pooling (Efficacy trial pooling-2; EFF-2). However, rare events and subgroups were assessed based on the largest available pooling, which included all 12873 patients with T2DM treated in trials with empagliflozin (SAF-5).

In SAF-5, 63.0% of the patients were male. The mean age was 59.6 years. The majority (64.8%) was diagnosed with type 2 diabetes for over 5 years. Most patients were White (62.0%) or Asian (33.8%); 3.6% were Black or African American. SAF-5 included a dedicated efficacy and safety study in patients with renal impairment, as well as a dedicated cardiovascular outcome study. Demographic and baseline data were generally similar across randomised groups. The frequencies of patients with treatment emergent AEs in the empagliflozin groups (68.1% for 10 mg and 69.5% for 25 mg) were similar to the frequency in the placebo group (68.6%) in SAF-5. The Medical Dictionary for Drug Regulatory Activities (MedDRA) preferred terms reported most often were hypoglycaemia, hyperglycaemia, nasopharyngitis, and UTI. Apart from hyperglycaemia, which was reported with a substantially lower frequency in the empagliflozin groups (4.3% for 10 mg and 4.7% for 25 mg) than in the placebo group (10.3%), the frequencies of most of these preferred terms were similar across the groups.

The frequencies of patients with AEs assessed by the investigator as drug related were higher in the empagliflozin groups (20.6% for 10 mg and 19.9% for 25 mg) than in the placebo group (15.2%). Genital infections were reported as drug related AEs more frequently in the empagliflozin groups than in the placebo group.

The frequencies of patients with AEs leading to discontinuation of study medication were similar for all groups (4.8% for empagliflozin 10 mg, 4.9% for empagliflozin 25 mg, and 5.3% for placebo). The MedDRA preferred term UTI was reported for higher proportions of patients in the empagliflozin groups than in the placebo group as AEs leading to discontinuation. The frequency of patients with AEs of severe intensity was slightly lower in the empagliflozin groups (6.1% for 10 mg and 6.5% for 25 mg) than in the placebo group (8.3%).

The frequencies of patients with SAEs (including fatal events) were lower in the empagliflozin groups (9.6% for 10 mg and 10.3% for 25 mg) than in the placebo group (12.7%) in SAF-5. Cardiac disorders were reported as SAEs with lower frequencies in the empagliflozin groups (2.1% for 10 mg and 2.3% for 25 mg) than in the placebo group (4.0%). The incidence rate per 100 patient years of patients with fatal AEs was lower with empagliflozin treatment (0.52; 41 deaths; including all doses) than with comparator treatments (0.78; 33 deaths; including placebo).

In pre-specified standardised MedDRA queries regarding hepatic injury, the frequencies were similar for all groups (1.2% for empagliflozin 10 mg, 1.4% for empagliflozin 25 mg, and 1.5% for placebo). There were more patients with liver enzyme elevation (ALT/AST ≥ 3x upper limit of normal (ULN) with total bilirubin ≥ 2x ULN or ALT/AST ≥ 10x ULN) in the empagliflozin groups (11 patients) than in the comparator groups (1 patient). However, no cases satisfied Hy's law and all cases could be explained by plausible causalities alternative to drug induced liver injury.

Effects on renal function were in general similar for all groups, based on the evaluation of renal AEs (with a pre-specified standardised MedDRA query) and laboratory parameters. For patients receiving empagliflozin, there was a small decrease in eGFR after the start of treatment (lowered by 2 to 3 mL/min/1.73 m^2 from baseline after 12 weeks); thereafter, eGFR value gradually returned to baseline over time (lowered by around 1 mL/min/1.73 m^2 from baseline after 1 year). This minimal change in eGFR was judged not to be of clinical relevance and was reversible after discontinuation of empagliflozin treatment. For patients with micro- or macroalbuminuria, empagliflozin treatment led to a greater reduction in albuminuria than placebo.

Empagliflozin treatment slightly increased haematocrit values (absolute change from baseline around 3%). Nevertheless, the increase in haematocrit was reversible after the discontinuation of empagliflozin treatment; the frequencies of patients with thromboembolic AEs did not increase with empagliflozin treatment (0.08% for 10 mg and 0.09% for 25 mg; 0.23% for placebo).

Empagliflozin treatment led to small dose dependent increases (around 0.1 mmol/L) in total cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol but no change in LDL/HDL cholesterol ratio. Empagliflozin treatment did not change electrolyte levels and there were no other significant changes in other laboratory parameters.

Safety of empagliflozin was demonstrated in a very large set (12873 patients) and a representative sample of patients with type 2 diabetes using a variety of antidiabetic background medications. Empagliflozin 10 mg or 25 mg qd demonstrated similar and favourable safety profiles.

First round benefit-risk assessment

First round assessment of benefits

The benefits of empagliflozin in the proposed usage are:

- Simple qd oral dosing.
- The sponsor has conducted a comprehensive program of PK interaction studies with drugs which are most likely to be co-administered with empagliflozin and these have revealed no evidence of significant interference by these drugs with empagliflozin PKs such as to necessitate any recommendations regarding dosage adjustment.
- The blood glucose lowering effect of empagliflozin is independent of insulin secretion or action. Empagliflozin's insulin independent mode of action results in a low risk of hypoglycaemia which was confirmed in the study comparing empagliflozin with glimepiride (Study 1245.28).
- In addition to reduction of HbA1c, empagliflozin treatment also helps reduce FPG and MDG levels.
- Statistically and clinically relevant reduction in body weight.

- Statistically and clinically relevant reduction in BP.
- Efficacy was shown in treatment naïveT2DM patients and when used in combination with metformin, combination with metformin + sulfonylurea, combination with basal insulins.
- Empagliflozin was also non-inferior to sitagliptin and glimepiride in terms of glycaemic control.
- Efficacy was also shown in T2DM patients with renal impairment, hypertension and CV risk factors.
- Of the patients with high HbA1c (> 10%) who received open label treatment with empagliflozin 25 mg qd for 24 weeks, 15.2% showed HbA1c < 7% after 24 weeks of treatment.
- Long term efficacy was adequately evaluated in patients and reduction in HbA1c, FPG, body weight and BP was maintained for up to 52 weeks.
- Empagliflozin was devoid of serious hypoglycaemic AEs usually associated with other oral antidiabetic agents.
- In a randomised, placebo controlled, active comparator, crossover study of 30 healthy subjects no increase in QTc was observed with either 25 mg or 200 mg empagliflozin.
- Empagliflozin demonstrated a favourable safety profile in a very large set of patients with type 2 diabetes using a variety of antidiabetic background medications.

First round assessment of risks

The risks of empagliflozin in the proposed usage are:

- Efficacy was not shown in patients with moderate renal impairment (Grade 3B with EGFR < 45 mL/kg/m^2) and in patients with severe renal impairment.
- As efficacy of the drug is dependent on renal function, it is essential to monitor renal function in the T2DM patients during administration of empagliflozin and it would be prudent to have set guidelines to monitor renal function during long term treatment with empagliflozin (similar to that included in the PI for the other approved SGLT2 inhibitor dapagliflozin).
- Genital infections, increased urination, UTIs, hypoglycaemia, and volume depletion were identified as listed side effects. Those events were mostly reported as mild in intensity and did not lead to discontinuation of trial drug.
- Potential safety concerns about use of empagliflozin with pioglitazone due to inconsistent results in the PK drug interaction studies between pioglitazone and empagliflozin.

First round assessment of benefit-risk balance

Empagliflozin is an orally administered, selective inhibitor of SGLT-2 in the kidney. It is intended for use in patients with T2DM. The blood glucose lowering effect of empagliflozin is independent of insulin secretion or action. Empagliflozin's insulin independent mode of action results in a low risk of hypoglycaemia. Further benefits of SGLT-2 inhibition include weight loss due to potential calorie loss through UGE and a reduction in BP due to a mild diuretic effect.

Overall, 13767 subjects were included and treated in the clinical trials constituting the development programme presented in this application. A total of 8506 patients with

T2DM were treated with empagliflozin (empagliflozin 25 mg: 4563 patients, empagliflozin 10 mg: 3311 patients). Of these, 6808 patients were treated with empagliflozin for at least 24 weeks, 4415 patients for at least 52 weeks, and 1486 patients for at least 76 weeks. With this number of patients and extent of exposure, the clinical programme exceeds the requirements of relevant guidelines and provides adequate and sufficient safety and efficacy information for the assessment of empagliflozin as treatment for type 2 diabetes in adults.

Treatment with empagliflozin 10 mg or 25 mg qd resulted in a robust improvement of glycaemic control with statistically significant and clinically meaningful reductions of HbA1c and FPG. The 4 pivotal trials demonstrated the superiority of both doses of empagliflozin to placebo after 24 weeks. In 3 of the 4 trials, the effects for the 25 mg dose were numerically larger than for the 10 mg dose. The effects were consistent across a range of different antidiabetic background regimens. Thus, empagliflozin improved glycaemic control as monotherapy and as add-on to metformin monotherapy, metformin plus sulfonylurea, and pioglitazone (with or without metformin).

Maximal efficacy of empagliflozin on glycaemic control was established 12 weeks after the start of treatment. Efficacy was sustained for at least 52 weeks, as shown in the double blind extensions of the 4 pivotal trials. The proportions of patients reaching the target HbA1c (< 7.0%) at week 24 were significantly larger for both empagliflozin doses than for placebo in each trial; treatment with empagliflozin 25 mg led to higher responder rates than treatment with empagliflozin 10 mg. In addition, significantly fewer patients in the empagliflozin groups required rescue medication than patients in the placebo groups. The results for HbA1c and FPG were further supported by reductions in mean daily glucose and postprandial glucose, which were investigated in 2 of the pivotal trials.

Empagliflozin also provided significant and clinically meaningful reductions in HbA1c compared with placebo in all other Phase III placebo controlled trials, that is, in patients treated with basal insulin, in patients with type 2 diabetes and hypertension, in patients with mild and moderate renal impairment, and in patients with increased cardiovascular risk (including a subpopulation of patients with increased cardiovascular risk on a background of metformin and DPP-4 inhibitor, with or without one additional oral antidiabetic agent). The HbA1c lowering effect of empagliflozin was generally consistent across various subgroups based on demographic factors or baseline characteristics.

Body weight reduction and optimum control of BP are 2 important unmet needs in the management of patients with type 2 diabetes. Empagliflozin treatment led to statistically significant and clinically meaningful reductions in body weight in all pivotal trials. Furthermore, significant and clinically meaningful reductions of SBP compared with placebo were achieved for empagliflozin 25 mg in each of the pivotal trials. For DBP, reductions were also observed but were smaller and not always significant compared with placebo. In an ABPM trial in patients with type 2 diabetes and hypertension, both doses of empagliflozin were superior to placebo in reducing 24-h SBP and 24-h DBP after 12 weeks of treatment. Weight and BP reductions of a magnitude similar to that in the pivotal trials were reached in the other supportive trials including the trials in patients with renal impairment or with high cardiovascular risk. Notably, in patients without hypertension, treatment with empagliflozin was not associated with an increased frequency of AEs indicative of hypotension. The weight and BP reductions were sustained throughout the short- and long-term trials. The effects of empagliflozin on body weight and BP are expected to modify cardiovascular risk factors and cardiovascular risk, and may translate into a benefit on the long-term micro- and macro-vascular complications of diabetes that extend beyond the effect on glycaemic control. This is being evaluated in the ongoing study in T2DM patients with CV risk factors (Study 1245.25).

Empagliflozin 25 mg was compared to the established antidiabetic drug glimepiride. In this double blind trial, empagliflozin was shown to provide non-inferior glycaemic control

to glimepiride (up to 4 mg daily) after 52 weeks of treatment. At the same time, empagliflozin was superior to glimepiride for several other clinically important endpoints, namely body weight reduction, a reduced occurrence of confirmed hypoglycaemic events, and for SBP and DBP reductions.

Metformin is the current standard first-line treatment for patients with type 2 diabetes. New antidiabetic drugs will therefore likely be employed as combination therapy, for example with metformin, or as monotherapy in patients for whom metformin is inappropriate. Sitagliptin is one of the few antidiabetic drugs with such a restricted monotherapy claim (in the EU). Therefore, empagliflozin efficacy was compared with that of sitagliptin in the pivotal monotherapy trial (1245.20) and its extension. Empagliflozin 25 mg qd showed significantly greater reductions in HbA1c, weight and BP than sitagliptin at week 52. The usefulness of empagliflozin in the monotherapy setting was further substantiated in a 12 week, double blind, placebo controlled Phase IIb trial with an open label (immediate release) metformin group. Long term data of up to 90 weeks from the open label extension of this trial showed sustained and similar improvements of glycaemic control with empagliflozin 25 mg and with metformin. These results suggest that empagliflozin may be an efficacious treatment option in patients for whom metformin is considered inappropriate. In this context, the added benefits of empagliflozin compared with the sulfonylurea glimepiride, which is also an alternative when metformin is inappropriate, are even more important.

In most of the trials, the 25 mg dose of empagliflozin showed better efficacy than the 10 mg dose. This was true for all endpoints (HbA1c, FPG, body weight, SBP, DBP). A higher proportion of patients reached the HbA1c target of < 7% with empagliflozin 25 mg than with empagliflozin 10 mg. Fewer patients treated with the high empagliflozin dose required rescue medication than patients treated with the low empagliflozin dose.

To support an integrated analysis of safety, the trial data were pooled to adequately analyse the different aspects of the safety profile of empagliflozin. The most relevant safety pooling for the benefit risk assessment of empagliflozin is SAF-3 (pool of pivotal trials with extensions, 2957 patients in total) as this pooling corresponds to the efficacy pooling EFF-2. However, rare events and subgroups were assessed based on the largest available pooling, which included all 12873 patients with T2DM treated in trials with empagliflozin (SAF-5). The overall exposure to empagliflozin (10 or 25 mg) was 1546 patient years (median treatment duration 369 days) in SAF-3 and 7828 patient years (median treatment duration 364 days) in SAF-5. The frequencies of premature discontinuation of trial medication were higher in the placebo group than in the empagliflozin groups (SAF-3: placebo: 17.1%; empagliflozin 10 mg: 10.8%; empagliflozin 25 mg: 12.8%). This was consistently observed across the different poolings, trials, and subgroup analyses, indicating that treatment with empagliflozin was generally satisfactory for patients.

The overall frequency of treatment emergent AEs was comparable between treatment groups (SAF-3: placebo: 74.1%; empagliflozin 10 mg: 71.8%; empagliflozin 25 mg: 70.1%). Investigator-assessed drug related events were more frequent in the empagliflozin treatment groups than in the placebo group, whereas AEs of severe intensity were more frequent in the placebo group. The frequencies of patients with serious AEs (including fatal events) in the empagliflozin groups were lower than in the placebo group in the pivotal trials with extensions (SAF-3: placebo: 7.4%; empagliflozin 10 mg: 7.1%; empagliflozin 25 mg: 5.8%). The incidence of fatal AEs was lower with empagliflozin treatment (SAF-5: 41 deaths, 0.5%, incidence rate 0.52 per 100 patient years) than with comparator treatments (including placebo; 33 deaths, 0.7%, 0.78 per 100 patient years).

MedDRA preferred terms reported most frequently as AEs were nasopharyngitis, UTI, hyperglycaemia, and hypoglycaemia; the frequency of most of these events was similar across the treatment groups. Hyperglycaemia was reported with a substantially lower

frequency in the empagliflozin groups (SAF-3: 5.5% for 10 mg and 4.5% for 25 mg) than in the placebo group (21.7%).

With regard to subgroups, there was no clear evidence for a major influence of any intrinsic or extrinsic factor on AE frequencies The safety laboratory data revealed no clear trends of clinical relevance in relation to the use of empagliflozin. Small increases of haematocrit were observed, but did not lead to an increased frequency of thromboembolic events. Small increases in lipid parameters (total cholesterol, HDL cholesterol, and LDL cholesterol) were seen for the empagliflozin groups (with differences to placebo ranging from 0.06 mmol/L to 0.13 mmol/L). But as no meaningful changes were seen for the LDL/HDL ratio and no safety signal was observed in the cardiovascular meta-analysis, the changes in lipid parameters are not considered clinically meaningful. Across all AE and laboratory analyses, differences between the two doses of empagliflozin investigated in Phase III trials (10 mg and 25 mg) were small and not always consistently observed across trials and poolings. Therefore, both doses are considered equally safe for the treatment of type 2 diabetes.

Overall, empagliflozin demonstrated a favourable safety profile in a very large set of patients with type 2 diabetes using a variety of antidiabetic background medications.

Empagliflozin was safe and efficacious in patients with type 2 diabetes as a monotherapy and in combination with other oral antidiabetic medications or insulin. Empagliflozin was also safe and efficacious in patients with type 2 diabetes and further co-morbidities like mild or moderate renal impairment, hypertension, or high cardiovascular risk. Empagliflozin 25 mg generally showed numerically better efficacy results than empagliflozin 10 mg, and both doses showed a good safety profile.

Hence, the overall benefit risk profile for empagliflozin 25 mg qd for the proposed indication is favourable.

First round recommendation regarding authorisation

It is recommended that empagliflozin 25 mg qd be approved for the proposed indication of *"as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus."* However, the approval is subject to a satisfactory response to the clinical questions (see below).

The clinical evaluator's recommended revisions to clinical aspects of the draft PI are beyond the scope of the AusPAR.

Clinical questions

Efficacy

1. The sponsors have not clarified if the dataset submitted to the USA and Canada was similar to that submitted to Australia and EU. Could the sponsors please clarify?

Safety

1. Module 2 (Clinical summary of safety) states that analysis of drug related AEs was performed for SAF-3 (pivotal study with extension), SAF-5 (all patients), and Study 1245.25. However, the results of drug related AEs were only provided for the SAF-5 and Study 1245.25; results for the pivotal studies SAF-3 group were not provided. Could the sponsors provide the results of drug related AEs in the pivotal studies group (SAF-3)?

2. In the pivotal studies, 12-lead ECGs were taken at baseline and at end of study. There is no data on ECG provided in the safety summary in Module 2 or in the individual study reports. Could the sponsors please clarify this?

Product Information: indications

The indications should provide details of how empagliflozin should be used in the different T2DM patients (as monotherapy, in combination with other oral antidiabetic agents and with basal insulin).

- Monotherapy
  Empagliflozin 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
  Empagliflozin 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
  Empagliflozin 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.

Could the sponsor please comment.

Second round evaluation of clinical data submitted in response to questions

Efficacy question 1

Sponsor's response

In the original submission, the applicant stated that the data set submitted to Australia was similar to the data set submitted to the EU. The applicant confirms that the data set submitted to Australia was also similar to the data set submitted to the USA and Canada in the original submission.

However, in the subsequent interactions with the health authorities in the EU and USA, the applicant proposed new dose recommendation and target population according to the feedback from the authorities, and following further assessment of clinical data. See CER Extract at Attachment 2 for details.

Evaluator's comments on sponsor's response

The evaluators agree with the sponsor's request for proposed new dose recommendation and target population. The modified dosing regimen ensures that the lowest effective dose is used in patients.

Safety question 1

Sponsor's response

Of the randomised and treated patients in SAF-3, the frequencies of patients with investigator-defined drug related AEs were higher in the empagliflozin groups (10 mg and 25 mg) than in the placebo group, and lower in the sitagliptin group than in the placebo group.

The frequencies of the most common investigator-defined drug related AEs at system organ class (SOC) level were in general higher in the empagliflozin groups than in the placebo group, and lower in the sitagliptin group than in the placebo group. At preferred term (PT) level, pollakiuria, polyuria, dysuria, thirst, vulvovaginal mycotic infection, vulvovaginal pruritus, and balanoposthitis were reported more frequently in the empagliflozin groups than in the other groups. UTI was less frequent in the empagliflozin groups and the sitagliptin group than in the placebo group. Hyperglycaemia was less frequent in empagliflozin groups than in the other groups. Weight decrease and dry mouth were reported more frequently in the empagliflozin 25 mg group than in the other groups. Hypoglycaemia was more frequent in the empagliflozin 10 mg group than in the other groups. The other most frequent investigator-defined drug related events (with a frequency of > 0.5% in any group) were reported with similar frequencies in all groups. In the open label empagliflozin 25 mg group, the most frequent investigator-defined drug related AE at SOC level was metabolism and nutrition disorders (hypoglycaemia most common).

Evaluator's comments on sponsor's response

Results of drug related AEs in the SAF-3 (pivotal study with extension) dataset was similar to that observed in the SAF-5 dataset and no new safety concerns were raised following review of this data.

Safety question 2

In the pivotal studies, 12-lead ECGs were taken at baseline and at end of study. There is no data on ECG provided in the safety summary in Module 2 or in the individual study reports. Could the sponsors please clarify this?

Sponsor's response

According to the protocol of all Phase III studies, 12-lead ECGs were taken at Visits 3 (randomisation) and Visit 7 (end of treatment) and as required. Clinically significant findings at the screening or randomisation visits were to be regarded as baseline conditions; new findings thereafter were to be recorded as AEs, if: they were not associated with an already reported AE, symptom or diagnosis, and the investigational drug was discontinued, reduced, or increased, or additional treatment was required.

Although no ECG data were provided in the study reports or in the summary documents submitted, the important and significant ECG findings were carefully captured and sent for independent adjudication. Summary of these ECG findings was provided in an interim cardiovascular meta-analysis report (U12-2463). The ECG source documents were to be stored at the investigational sites. Copies of ECGs for patients who had ECG findings recorded as AEs were to be digitised and archived at Boehringer Ingelheim.

To systematically address the cardiovascular (CV) safety of empagliflozin treatment, an independent clinical event committee (CEC) was established for the central adjudication of potential CV endpoint events. For all Phase III trials, the CEC reviewed all reported trigger events. The criteria for a trigger event to be sent for adjudication were defined in the CEC charter. Among the trigger events defined in the charter, those related to ECG findings are: cardiac fibrillation, ECG electrically inactive area, ECG signs of myocardial ischaemia,

electrocardiogram Q wave abnormal, electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, electrocardiogram repolarisation abnormality, electrocardiogram ST segment abnormal, electrocardiogram ST segment depression, electrocardiogram ST segment elevation, electrocardiogram ST-T segment abnormal, electrocardiogram ST-T segment depression, electrocardiogram ST-T segment elevation, electrocardiogram T wave abnormal, electrocardiogram T wave inversion, electrocardiogram U-wave abnormality, electrocardiogram U-wave biphasic, exercise electrocardiogram abnormal, long QT syndrome, long QT syndrome congenital, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, and ventricular tachyarrhythmia.

Adjudication was performed without knowledge of the treatment assignment of any patient; if confirmed by the CEC, patients with trigger events were adjudicated to have CV endpoint events as defined in the CEC charter.

The CEC-confirmed CV endpoint events were summarised in the CV meta-analysis (interim report see (U12-2463)), which included data from completed trials (randomised double blind Phase II and Phase III trials with a treatment duration of longer than 12 weeks) and on-going trials (randomised double blind Phase III trials that had pre-planned interim database locks). The primary endpoint of the meta-analysis is the 4-point MACE (a composite of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalisation due to unstable angina); the secondary endpoint is the 3-point MACE (cardiovascular death, non-fatal MI, and non-fatal stroke).

The applicant is also conducting a long term CV outcome study (1245.25), which is placebo controlled and includes patients with type 2 diabetes and high CV risk. The primary endpoint was the 3-point MACE; the secondary endpoint was the 4-point MACE. The interim CV data of this trial were included in the interim meta-analysis report, both as part of the meta-analysis and analysed exclusively at the study level. Additionally, silent myocardial infarction is defined as a further secondary endpoint in the 1245.25 study protocol. By the end of the study, all available ECGs will be assessed for silent myocardial infarctions and this secondary endpoint will be reported in the final report.

Furthermore, a Phase I study (1245.16 (U11-1908)) tested the effect of empagliflozin treatment (single dose) on the QT(c) interval in 30 healthy subjects. The randomised, placebo controlled, double blind, crossover study included moxifloxacin as a positive control. The study showed that single oral doses of empagliflozin 25 mg (therapeutic dose) and 200 mg (supra-therapeutic dose) were not associated with a QT(c) interval prolongation and that these doses were safe and well tolerated. Furthermore, 12-lead ECGs were regularly performed in all Phase I studies in the empagliflozin clinical development programme; no clinically relevant findings in the ECGs were observed.

In summary, ECGs data were carefully collected throughout the clinical development programme. Clinically significant ECG findings were properly captured and were recorded as AEs. All CV events, including ECG findings, were adjudicated centrally and independently, and summarised in a CV meta-analysis across the Phase II and III trials. Therefore, the Applicant believes that the analyses of 12-lead ECGs data in the empagliflozin clinical development programme have been adequate.

Evaluator's comments on sponsor's response

The sponsor's response is acceptable. The final results of the long-term CV outcome Study 1245.25 should be submitted on completion.

Product Information: indications

Sponsor's response

In response to the evaluator's request for comment, Boehringer Ingelheim proposes the following alternative wording to the proposed indication:

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control for patients in whom use of metformin is considered inappropriate due to intolerance.*
>
> *Add-on combination therapy: In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials).*

The PI has been amended to include this revised wording.

Evaluator's comments on sponsor's response

The above proposed indication is acceptable.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of empagliflozin in the proposed usage are unchanged from those identified in the *First round assessment of benefits*.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of empagliflozin in the proposed usage are unchanged from those identified in the *First round assessment of risks*.

Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit risk balance of empagliflozin in the proposed usage is favourable.

Second round recommendation regarding authorisation

It is recommended that empagliflozin be approved for the following modified indication proposed by the sponsors in their response to the TGA request for comment and further information:

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.*
>
> *Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials)."*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), RMP Version 1 (U13-1175-01) (in EU-RMP format) (dated 01/02/2013, data lock point (DLP) 31/08/2012) and Australian Specific Annex (ASA) Version 1.0 (ASA U13-1175-01) (dated 24/04/2013, DLP not given), 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 9.

Table 9: Summary of ongoing safety concerns

Ongoing safety concerns	
Important Identified Risks	UTI; Volume depletion.
Important Potential Risks	Malignancy; Renal impairment.
Important Missing Information	Paediatric use; Elderly use; Pregnancy; Breast-feeding of neonates/infants; Obese patients who do not have type 2 diabetes mellitus

Pharmacovigilance plan

The sponsor proposes only routine pharmacovigilance activities for important identified and potential risks and missing information.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all ongoing safety concerns. The sponsor makes the following statement in the RMP regarding the need for additional risk minimisation activities: '*No additional risk minimisation measures are planned.'*

Reconciliation of issues outlined in the RMP report

A summary of the OPR's recommendations from the first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses is below:

Table 10: Reconciliation of issues outlined in the RMP evaluation report

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
Recommendation 1: The sponsor should add the following Ongoing Safety Concerns (Important Identified Risks and Important Potential Risks):		
Urosepsis;	Cases with UTI were identified using the Boehringer Ingelheim customised MedDRA query (BIcMQ) 'UTI' which included the preferred term (PT) 'urosepsis'. In addition further analyses looking at complicated UTI (acute pyelonephritis, urosepsis) was conducted. This included evaluating cases of sepsis with a possible urinary tract source (and not previously reported as PT 'urosepsis'). Cases of complicated UTI were very rare, with similar frequencies. The RMP identifies UTI as an important identified risk which includes urosepsis. The PI has been amended and includes text with reference to UTI under Special warnings and precautions. The sponsor is of the opinion that urosepsis is sufficiently covered by UTI and no RMP or PI amendment is warranted at present.	This is considered acceptable.
Genital infection;	The sponsor agrees to include genital infections as important identified risk in the RMP.	This is considered acceptable.
Hypoglycaemia;	The risk of hypoglycaemia during empagliflozin administration is considered to be low, as other renal glucose transporters (such as SGLT-1 and GLUT) can still reabsorb glucose, and the liver may increase hepatic gluconeogenesis if blood glucose falls to hypoglycaemic levels. However, the sponsor agrees to include hypoglycaemia for empagliflozin when administered with insulin	This is considered acceptable.

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
	and/or sulfonylurea as important potential risk in the RMP.	
Increased haematocrit;	The sponsor agrees that treatment with empagliflozin may result in a small mean increase in haematocrit; however, no association could be established between this small increase and thromboembolic events. Increased haematocrit may be caused by erythrocytosis, for example, due to primary or secondary polycythaemia vera, hypoxaemic conditions (such as chronic obstructive pulmonary disease (COPD)) or by haemoconcentration, the latter as likely pathophysiology in empagliflozin treated patients. Given this root cause the potential clinical consequence of increased haematocrit is considered adequately addressed under the identified risk of volume depletion.	This is not considered acceptable. An increase in haematocrit is associated with arterial and venous thromboembolic events. Not all haematocrit changes are due to volume depletion. In order to adequately monitor this risk, the 'Increased haematocrit' needs to be included as an Ongoing Safety Concern.
Renal failure;	The sponsor agrees to include renal impairment as important potential risk in the RMP. The RMP was updated accordingly	This is considered acceptable.
Off-label use (including weight loss and type 1 diabetes mellitus).	The sponsor agrees to amend the RMP to include off-label use for weight loss in non-T2DM patients as well as off-label use in T1DM (type 1 diabetes mellitus) patients as an important potential risk.	This is considered acceptable.
Recommendation 2: The sponsor should add the following Ongoing Safety Concerns (Important Missing Information):	The inclusion of the suggested topics as missing information was discussed and evaluated regarding their relevance for empagliflozin. The sponsor agrees to include concomitant use with GLP-1 analogues and patients with BMI > 45 kg/m^2 as missing information. The sponsor considers patients with severe renal impairment, hepatic impairment, not as missing information. The RMP was adapted accordingly.	This is considered acceptable.

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
Patients with severe renal impairment;	The information on empagliflozin's safety in patients with severe renal impairment is limited, however due to the lack of efficacy in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), empagliflozin is not recommended for these patients (U13-1175) as reflected in the PI. Therefore the sponsor does not consider this topic as missing information.	The sponsor's request not to include this concern as missing information is acceptable. In the EU-RMP, Version 1.1, the sponsor states: 'Efficacy is not established with patients with an estimated glomerular filtration rate (eGFR) < 45mL/min/1.73 m^2 or end stage renal disease, thus the benefit risk implications for that special population contraindicates its use. As a result, the PI should state that empagliflozin is not indicated in patients with an eGFR < 45 mL/min/1.73 m^2.
Patients with hepatic impairment;	Increased empagliflozin exposure in patients with hepatic impairment was not considered to be clinically relevant. Based on the PK data, dose adjustments of empagliflozin are not warranted in patients with any degree of hepatic impairment (U13-1124) as reflected in the PI.	This is considered acceptable. However, the known effects (AUC increase) in hepatic impairment needs to be communicated in the PI
Concomitant use with GLP-1 analogues;	The sponsor agrees to include concomitant use with GLP-1 analogues and patients with BMI > 45 kg/m^2 as missing information.	This is considered acceptable.
Patients with BMI > 45.	The applicant agrees to include concomitant use with GLP-1 analogues and patients with BMI > 45 kg/m^2 as missing information.	This is considered acceptable.

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
Recommendation 3: The sponsor should conduct appropriate and relevant additional pharmacovigilance activities to investigate the Important Potential Risks further or assign existing appropriate and relevant additional pharmacovigilance activities to these Ongoing Safety Concerns.	The following are the current proposed pharmacovigilance activities for the important potential risks: **Malignancy** Routine pharmacovigilance. **Renal impairment** Routine pharmacovigilance. The sponsor proposes to conduct a post-authorisation safety study (PASS) to evaluate the risk of acute renal failure in empagliflozin treated patients. **Liver injury** Routine pharmacovigilance. The sponsor proposes to conduct a PASS to evaluate the risk of liver injury (such as acute hepatic failure, resulting in hospitalisation) in empagliflozin treated patients **Hypoglycaemia (with insulin and/or sulfonylurea)** Routine pharmacovigilance. **Off-label use for weight loss in non-T2DM patients** Routine pharmacovigilance. The sponsor proposes to conduct a Drug Utilisation Study (DUS) to assess the characteristics of patients initiating empagliflozin therapy and to quantify the extent of the off-label use in the empagliflozin-treated population'	This is considered acceptable.
Recommendation 4: The sponsor should conduct appropriate and relevant additional pharmacovigilance activities to investigate patients with severe renal impairment and patients with hepatic impairment further or assign existing appropriate and	The PI has been amended and specifies that empagliflozin is not recommended for use in patients with persistent eGFR < 45 mL/min/1.73 m^2. The applicant is of the opinion that patients with severe renal impairment and patients with hepatic impairment are not important missing information. Please see response to Recommendation 2 above.	This is considered acceptable.

Recommendation in RMP evaluation report	Summary of sponsor's response	OPR evaluator's comment
relevant additional pharmacovigilance activities to this Important Missing Information.		
Recommendation 5: An education programme is necessary as an additional risk minimisation activity to further mitigate the risks associated with empagliflozin. Components of the program have been suggested.	In summary, in a very large set (12873 patients) and a representative sample of patients with T2DM using a variety of antidiabetic background medications, empagliflozin 10 mg or 25 mg qd demonstrated similar and favourable safety profiles. The overall benefit risk balance is positive when used within the proposed indication. The following identified risks infection may be observed in patients treated with empagliflozin: volume depletion, urinary and genital tract infection. The sponsor is of the opinion that these risks are sufficiently handled with routine risk mitigation measures and adequately addressed in the amended PI. Any additional risk mitigation activities would add unnecessary burden on patients and prescribers.	SGLT-2 inhibitors are a new class of antidiabetic agents with specific ongoing safety concerns and there is limited Australian experience with this class of drugs, especially when considering its long term use in an often co-morbid population. For these reasons education programs have been requested for all SGLT-1 inhibitors. In the interest of regulatory consistency, the sponsor should conduct an education programme, with components as suggested by the OPR evaluator. The recommendation remains.

The remaining OPR recommendations relate to revisions to the draft PI and Consumer Medicine Information (CMI) documents in the context of routine risk minimisation activities. Details of these are beyond the scope of the AusPAR.

Summary and recommendations

The sponsor's response to the TGA s request for information has adequately addressed some of the issues identified in the RMP evaluation report but has not adequately addressed others (see Table 10 above).

Outstanding issues

Summary of outstanding issues:

Recommendations in regard to pharmacovigilance activities

'Increased haematocrit' needs to be included as an Ongoing Safety Concern.

Recommendations in regard to risk minimisation activities

Details of recommended revisions to product literature in the context of risk minimisation activities are beyond the scope of the AusPAR.

SGLT-2 inhibitors are a new class of antidiabetic agents with specific ongoing safety concerns and there is limited Australian experience with this class of drugs, especially when considering its long term use in an often co-morbid population. For these reasons education programs have been requested for all SGLT-1 inhibitors. In the interest of regulatory consistency, the sponsor should conduct an education programme, with components as suggested by the OPR evaluator.

Clinical and nonclinical comments on the safety specifications

The sponsor should incorporate any changes proposed by the nonclinical evaluator (see below).

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator made the following first-round comment in regard to safety specifications in the draft RMP:

> 'The Safety Specification in the draft Risk Management Plan is satisfactory.'

The clinical evaluator made the following second-round comment in regard to safety specifications in the draft RMP:

> 'Inclusion of "use with GLP-1 analogues" as "missing information" in the draft RMP is supported.
>
> Due to lack of consistent results in the two PK drug interaction studies between pioglitazone and empagliflozin, it is recommended that concomitant treatment of pioglitazone be monitored and included in the draft RMP.
>
> All other issues related to the draft RMP should be addressed by the RMP evaluator.'

Nonclinical evaluation report

The nonclinical evaluator made the following summary comment in regard to safety specifications in the draft RMP:

> 'The evaluator for the most part agrees with results and conclusions drawn from the nonclinical program for empagliflozin detailed in the sponsor's draft RMP.'

The nonclinical evaluator has suggested changes to the RMP, including:

- Toxicity observed at clinically relevant exposures in rodents;
- Renal lesions observed in rodents at all doses without NOAEL;
- Empagliflozin (and/or its metabolites) excretion in milk;
- Insufficiently characterised risks in a paediatric population;
- Inaccurate safety conclusions with regard to nonclinical data;
- Other irregularities.

> **OPR evaluator comment:** The OPR evaluator supports the changes proposed by the nonclinical evaluator.

Key changes to the updated RMP

Risk Management Plan Version 1 (U13-1175-01) (in EU-RMP format) (dated 01/02/2013, DLP 31/08/2012) and ASA Version 1.0 (ASA U13-1175-01) (dated 24/04/2013, DLP not given) has been superseded by: RMP Version 1.1 (U13-1175-02) (in EU-RMP format) (dated 02/10/2013, DLP 31/08/2012) and ASA Version 1.1 (ASA U13-1175-02) (dated 20/12/2013, DLP not given). Key changes from the versions evaluated at Round 1 are summarised below:

Table 11: Summary of key changes between RMP versions 1 and 1.1

RMP: Key changes from version 1.0 to version 1.1	
Safety specification	Important Identified Risks: • Genital infection (added). Important Potential Risks: • Liver injury (added); • Hypoglycaemia (with insulin and/or sulfonylurea) (added); • Off-label use (added). Important Missing Information: • 'Elderly use' replaced by 'Older people'; • 'Pregnancy' and 'Breast-feeding of neonates/infants' replaced by 'Pregnancy/breast-feeding'; • Dyslipidaemia (added); • Long term safety (particularly cardiovascular) (added); • Concomitant use with GLP-1 analogues (added).
Pharmacovigilance activities	Updates to include new Ongoing Safety Concerns New additional pharmacovigilance activities: • Long-term CV safety Study 1245.25; • Proposed DUS to assess potential off-label use; • Proposed PASS to assess the risk of urinary tract and genital infection; • Proposed PASS to assess the risk of renal and liver injury.
Risk minimisation activities	Updates to include new Ongoing Safety Concerns

RMP: Key changes from version 1.0 to version 1.1	
ASA	Updates to include new Ongoing Safety Concerns

Recommendation and conditions of registration

- Any changes to the RMP that were agreed to by the sponsor become part of the RMP, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.
- Once a satisfactory RMP has been submitted, the following is recommended as a condition of registration:
  - Implement Risk Management Plan Version 1.1 (U13-1175-02) (in EU-RMP format) (dated 02/10/2013, DLP 31/08/2012) and Australian Specific Annex Version 1.1 (ASA U13-1175-02) (dated 20/12/2013, DLP not given), and any future updates (where TGA approved) as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Quality

All chemistry and quality control issues have been satisfactorily resolved. Stability data show that the drug substance is stable and justify the proposed 36 month retest period when stored in the proposed packaging at below 30°C.

The evaluator discusses 3 bioavailability studies:

- Study 1245.79/U12-1744-01

This study was to investigate of the effect of food on the bioavailability of a 25 mg empagliflozin tablet and assess dose proportionality between 10 mg and 25 mg empagliflozin tablets in an open, randomised, single dose, three-period cross-over study in healthy male and female subjects. Administration of empagliflozin formulation with food resulted in a decrease in empagliflozin exposure, with $AUC_{0-\infty}$ 16% lower and Cmax 37% lower under fed conditions compared with fasted conditions. The products are dose proportional between the 10 mg and 25 mg empagliflozin tablets.

- Study 1245.3/U08-1977-01

This study also assessed food effect on PK and the extent of absorption of a single dose empagliflozin tablet (TF-I) in healthy subjects where there was a small decrease in empagliflozin exposure, with $AUC_{0-\infty}$ being 10% lower and Cmax being 29% lower under fed compared to fasted condition.

- Study 1245.51/U11-1756-01

This study investigated the relative bioavailability of empagliflozin when administered as 25 mg empagliflozin FF compared with 25 mg empagliflozin TF-II. They were found to be bioequivalent.

No absolute bioavailability study was submitted. The evaluator states that the justification submitted by the sponsor is acceptable from a chemistry point of view.

Overall, the evaluator recommends approval from a chemistry perspective. This submission has not been considered by PSC.

Nonclinical

The evaluator states 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).

Empagliflozin is highly selective for SGLT2 and with no off-target activities predicted at the proposed clinical dose. Primary pharmacology studies showed improved glucose tolerance in diabetic and obese animals and increased urinary glucose secretion at doses similar to the proposed clinical dose thus supporting the proposed dose and the proposed monotherapy indication. Combination with other oral hypoglycaemic agents showed an additive effect.

No clinically significant off-target activities are predicted based on secondary pharmacology studies.

The PK profile in mice, rats and dogs was considered similar to that of humans and was considered an appropriate model to assess toxicity in humans.

Empagliflozin is not expected to alter the PK of co-administered drugs via human CYP450 isoenzyme interactions. Inhibitors/inducers of OAT3, OATP1B1 and OATP1B3 could potentially alter the in vivo disposition of empagliflozin. In rats, no consistent PK interactions were evident with empagliflozin and metformin.

Empagliflozin showed low order acute toxicity orally in rodents. Repeat dose toxicity studies achieved high exposure in mice, rats and dogs. There were exaggerated primary pharmacological effects. There were secondary effects associated with SGLT2 inhibition (changes in the liver, pancreas and adrenals, other clinical chemistry changes and the risk of UTIs) or off-target effects on SGLT1 (gastrointestinal toxicity, effects on bone production and vascular mineralisation). The evaluator states that this is unlikely to be of clinical significance.

The evaluator mentions other findings not seen with other drugs in this class: degenerative changes in the kidneys of male mice (single cell necrosis, tubular atrophy, tubular karyomegaly, tubular hypertrophy, cysts, cystic tubular hyperplasia and atypical tubular hyperplasia). A NOEL was not established. Mechanistic studies suggest that these are due to metabolites not seen in humans. Exposures at the NOEL (for degenerative kidney lesions) in female mice, rats and dogs are reasonably high, ranging from 40 to 240 times the clinical AUC.

Repeat dose toxicity studies with metformin and linagliptin did not reveal new or exaggerated effects.

Empagliflozin was not genotoxic in the standard battery of tests.

No treatment related increase in tumour incidence was observed in female mice or female rats in approximately 2-year oral carcinogenicity studies. An increased incidence of renal atypical tubular hyperplasia, renal tubular adenomas and carcinoma was seen in male

mice at doses resulting in exposures 45 times the clinical AUC. These were attributed to metabolites not seen in humans.

The evaluator states that, *"high doses of empagliflozin did not affect male or female fertility in rats. Empagliflozin was shown to cross the placenta barrier only at very low levels and is excreted into milk. Adverse embryofetal effects in rats and rabbits were only seen at maternotoxic doses which resulted in high systemic exposures. Following maternal exposure, postnatal development in rats was impaired"*. As with others in the pharmacological class, empagliflozin should be considered to have a possible adverse effect on the developing kidney.

The evaluator mentions that the findings in the toxicity studies of clinical relevance are glucosuria, osmotic diuresis, effects on body weight and a risk for UTIs.

There are no objections on nonclinical grounds to the registration of Jardiance for the proposed monotherapy indication and combination therapy with linagliptin or metformin. The evaluator states that support (in particular with regards to safety) for combinations of empagliflozin with all other possible glucose lowering agents will need to rely solely on clinical data.

Clinical

Pharmacology

Pharmacokinetics

There are 14 PK studies of relevance; in addition, 15 interaction studies were included.

Absorption

No absolute bioavailability studies are submitted. The sponsor has addressed the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Section 4 which deals with justifications for not conducting bioavailability studies and the evaluator opines that this is a reasonable justification.

The studies revealed linear PK following single oral doses over the dose range from 0.5 mg to 800 mg in healthy volunteers. Over the dose range studied, empagliflozin exposure ($AUC_{0-\infty}$ and Cmax) increased in a roughly dose proportional manner. Empagliflozin was rapidly absorbed reaching peak levels after a median tmax of 1 to 2 h. After reaching peak levels, plasma concentrations declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. The mean t½ for doses 10 mg and above ranged from approximately 10 to 13 h.

After multiple oral dosing, empagliflozin reached steady state by Day 5. The PK of multiple dosing was similar to that of the single dose PK. The evaluator mentions that, *"the proportion of unchanged parent compound excreted in urine at steady state was independent of the dose and averaged approximately 18% of dose. Renal clearance of empagliflozin at steady state ranged from 36 to 37 mL/min. Empagliflozin exposure increased proportionally with an increase in dose over the dose range 2.5 to 100 mg after repeated dosing at steady state."* There were no clinically relevant differences in empagliflozin PK between healthy volunteers and patients with T2DM.

The evaluator also mentions that administration of 25 mg empagliflozin after intake of a high fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin PK was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

The apparent steady state volume of distribution was estimated to be 73.8 L, based on a population PK analysis. Following administration of an oral ^{14}C-empagliflozin solution to healthy subjects, the RBC partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism

There were no major metabolites. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by UGT2B7, UGT1A3, UGT1A8 and UGT1A9. The most abundant metabolites of empagliflozin were 3 glucuronide conjugates (3.3 to 7.4% of plasma radioactivity).

Elimination

Consistent with half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady state. Following administration of an oral ^{14}C-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Bioequivalence between clinical trial and final marketing formulation

The evaluator states that, *"all 3 formulations used in the empagliflozin clinical development program had the same qualitative composition. TF-I and TF-II were uncoated tables, and FF is a film coated tablet with a hypromellose based standard film coat. In vitro dissolution profiles depict immediate release characteristics and were similar for TF-II) and FF. Bioequivalence between the proposed commercial formulation and the TF-II formulation used in earlier clinical trials was demonstrated unequivocally. The 90% confidence intervals for the geometric mean ratios of both $AUC_{0-\infty}$ and Cmax were within the standard bioequivalence criteria of 80% to 125%"*.

Renal impairment

In patients with mild (eGFR: < 90 mL/min/1.73 m^2), moderate (eGFR: < 60 mL/min/1.73 m^2) or severe (eGFR: < 3 0 mL/min/1.73 m^2) renal impairment and patients with kidney failure/ESRD patients [study 1245.12], AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to patients with normal renal function (eGFR: > 90 mL/min/1.73 m^2); this was seen in Study 1245.36 where a single dose of 50 mg empagliflozin was used. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD. Plasma Cmax of empagliflozin was roughly 20% higher in subjects with mild and severe renal impairment as compared to patients with normal renal function. Based on these results no dosage adjustments were required in those with mild or moderate renal impairment. The same study revealed that there was loss of efficacy in those with severe renal impairment.

Hepatic impairment

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and Cmax by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function, in Study 1245.13.-A single oral dose of 50 mg of empagliflozin was used in 36 subjects. In addition, the population PK analysis showed that elevations of liver enzyme levels (AST, ALT, ALP and LDH) had no statistically significant impact on the apparent oral clearance of empagliflozin. The increase in exposure with increased degree of hepatic impairment was less than 2 fold: this magnitude does not affect the PD parameter of UGE. The evaluator states that this magnitude is of limited clinical relevance and hence, recommends no dose adjustment.

Interaction studies

Several drug interaction studies have been conducted. The following observations are made:

- No significant interaction with metformin was seen in a Phase I, open label, randomised, multiple dose, crossover study, 1245.6.
- No significant interaction was seen with glimepiride 1 mg in 16 healthy volunteers in Study 1245.7. However, this study used only a single dose of glimepiride.
- Two studies (1245.17 and 1245.50) examined interaction with pioglitazone. The former study used empagliflozin 50 mg and pioglitazone 45 mg daily in a multidose regimen. There was no change in the PK of empagliflozin observed in Study 1245.17; however, the AUC and Cmax increased for pioglitazone. AUC for the pioglitazone metabolites M-III and M-IV also increased. In the latter study, the AUC for pioglitazone was lower with concomitant use of empagliflozin. Due to inconsistent results across these two studies, the evaluator recommends caution in relation to concomitant use. A precautionary statement as per the dapagliflozin PI is recommended: empagliflozin should not be recommended for use in patients concomitantly treated with pioglitazone. This issue was addressed by the sponsor in their response to the Delegate's Overview (see below).
- Study 1245.27 did not reveal clinically significant interaction with empagliflozin 50 mg and sitagliptin 100 mg; (this was a multidose study).
- Study 1245.18 examined the PK effects of empagliflozin on warfarin. No clinically significant interaction was seen. The effects of digoxin on the PK of empagliflozin were evaluated in 1245.40 No clinically significant effect was seen.
- Oral contraceptives: Microgynon (Study 1245.41): The plasma concentration time profiles and other PK parameters of both ethinylestradiol and levonorgestrel were similar in both treatments groups (that is, with and without empagliflozin).
- Study 1245.43 evaluated the relative bioavailability of a single dose of empagliflozin (25 mg) when given alone compared with co-administration with a single dose of the model P-glycoprotein inhibitor verapamil (120 mg). The PKs of empagliflozin were similar when empagliflozin was administered alone or with verapamil. This study did not investigate the effect of empagliflozin on verapamil.
- In Study 1245.45, the PKs of empagliflozin were similar when empagliflozin was administered alone or with ramipril. Similarly, the PK of ramipril and ramiprilat were similar when ramipril was administered alone or with empagliflozin.
- In Study 1245.58, empagliflozin exposure was higher when co-administered with gemfibrozil compared to empagliflozin alone; $AUC_{0-\infty}$ of empagliflozin was roughly 59% higher (geometric mean ratio (GMR): 158.50%; 90% CI: 151.77 to 165.33%) during the combined treatment than during treatment with empagliflozin alone. The evaluator recommends caution when concomitantly administered.
- Results from Study 1245.63 indicate that there is no clinically relevant drug-drug interaction between empagliflozin (25 mg) and simvastatin (40 mg) and no dose adjustments for either drug are necessary when co-administered. This was a single dose study only.
- Single doses of empagliflozin 25 mg and rifampicin and probenecid did not reveal clinically relevant changes in Study 1245.83.

Population PK analysis

A population PK analysis was also conducted based on Phase I studies. This data set comprised 186 patients contributing a total of 5591 plasma concentrations. The typical population PK estimates were consistent with PK analysis from individual studies. A population PK analysis was also conducted in T2DM patients. This data set comprised 2761 patients contributing 12, 503 plasma concentrations. The effect of BMI, eGFR, age, female, Asian race on clearance and AUC_{ss} were examined. There was no clinically significant effect seen.

PK in special patient populations

The evaluator mentions that the PK of empagliflozin has not been evaluated in the paediatric population. Based on population PK analysis, there were no changes in empagliflozin PK in elderly patients; gender, race, BMI also did not have any clinically relevant effect on empagliflozin PK.

Pharmacodynamics

Five studies and a population PK/PD analysis were considered.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR.

Oral administration of empagliflozin resulted in a dose dependent increase in UGE. In healthy volunteers (Study 1245.2), UGE was higher with all doses (0.5 mg to 800 mg) compared with placebo. Empagliflozin inhibited reabsorption of < 40% of filtered glucose with single daily doses up to 10 mg and approximately 40 to 60% of filtered glucose at higher doses, with the effect reaching a plateau at around the 100 mg dose. Empagliflozin administration resulted in increased UGE in patients with T2DM (Study 1245.4). Empagliflozin inhibited reabsorption of 39%, 46%, 58%, and 64% of filtered glucose with 2.5, 10, 25 and 100 mg qd doses, respectively. Increased UGE with empagliflozin treatment did not result in clinically relevant changes in urine volume. In patients with T2DM, all empagliflozin dose groups showed reductions in plasma glucose compared to placebo. Declines in FPG were observed immediately after the first dose of empagliflozin and were maintained over the entire treatment duration. After 4 week treatment, FPG decreased by approximately 44 mg/dL, 34 mg/dL and 29 mg/dL with 10 mg, 25 mg, and 100 mg empagliflozin qd, respectively, compared to 4 mg/dL with placebo.

Overall, in patients with T2DM, UGE increased immediately following the first dose of empagliflozin and is continuous over the 24 h dosing interval. Increased UGE was maintained at the end of 4 week treatment period, averaging approximately 78 g/day with 25 mg empagliflozin qd. Increased UGE resulted in an immediate reduction in plasma glucose levels in patients with T2DM.

Study 1245.16 did not reveal any clinically significant effect on QT interval.

Dose selection studies

Two studies are discussed (1245.9 and 1245.10).

Study 1245.9 was a randomised, parallel group study of empagliflozin 5 mg, 10 mg and 25 mg administered orally qd over 12 weeks compared double blind to placebo, as monotherapy, with an additional open label metformin arm in type 2 diabetic patients with insufficient glycemic control. Inclusion criteria are listed by the evaluator. The main criterion was T2DM with HbA1c ≥ 6.5 to ≤ 9.0% (those on treatment) or HbA1c > 7.0 to ≤ 10.0% (treatment naïve).

A total of 408 patients were randomised to 1 of the 5 treatment arms in a 1:1:1:1:1 ratio. Overall, 52.0% of the patients were male, 63.8% were white and 34.5% were Asian. The mean (SD) age was 57.5 (9.8) years, HbA1c 7.9% (0.8%), and BMI 29.0 (4.6) kg/m^2.

For all 3 blinded empagliflozin treatment groups, the reduction in HbA1c was statistically significant and clinically meaningful, compared with placebo (5 mg: -0.52%, 10 mg: -0.57%, 25 mg: -0.72%). The open label arm of metformin had been included in the trial as a sensitivity measure and there was no direct comparison between efficacy of metformin and empagliflozin. There was a dose related reduction in FBG also.

Study 1245.10 was also of similar design using empagliflozin doses 1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) administered orally qd over 12 weeks compared double blind to placebo with an additional open label sitagliptin arm in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy. 495 patients who were randomised; the baseline demographics was similar between groups. Overall, majority of the patients were male (50.6%), non-Hispanic white (84.6%) with mean (SD) age was 58.3 (8.8) years, HbA1c 7.9% (0.7%), and BMI 31.4 (4.5) kg/m^2.

All 5 doses of empagliflozin showed statistically significant placebo corrected decrease in HbA1c, with largest decreases in the empagliflozin 10 mg (-0.71%) and 25 mg dose (-0.70%) with no further reduction with the 50 mg dose. There was also a statistically significant change in the FPG (with all doses except 1 mg).

The evaluator mentions that based on the analysis of the primary endpoint and some of the important secondary endpoints in the 2 dose ranging studies discussed above, both 10 mg and 25 mg doses of empagliflozin were most efficacious in regard to HbA1c and FPG lowering with the 50 mg dose showing no further increase in efficacy and agrees with the choice of 10 mg and 25 mg being used in the Phase III studies.

Clinical efficacy

There were 4 pivotal studies. One was a monotherapy study (1245.20). Three were add-on therapy (1245.19 and 1245.23); Study 1245.23 was, in fact, 2 separate studies using a single trial number.

Monotherapy (Studies 1245.20 and 1245.38)

The pivotal study is supported by findings from the Phase II study that was conducted in Japan. The latter is discussed briefly after the pivotal study discussion.

Study 1245.20 is was a double blind, placebo controlled study investigating empagliflozin 10 mg or 25 mg compared with placebo and sitagliptin 100 mg qd for 24 weeks. The study also had an open label arm to assess the efficacy and safety of empagliflozin 25 mg qd in patients with type 2 diabetes and very poor glycaemic control (HbA1c > 10%). The treatment groups were randomised on 1:1:1:1 ratio.

Inclusion criteria

Drug naïve patients with T2DM and insufficient glycaemic control (HbA1c ≥ 7.0% and ≤ 10.0%; with a BMI ≤ 45 kg/m^2) were eligible to enrol. Patients with an HbA1c of > 10% and fulfilling all remaining inclusion criteria were eligible for inclusion in the empagliflozin 25 mg open label arm. Exclusion criteria are listed in the CER.

Efficacy endpoints

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and BP (SBP and DBP) after 24 weeks of treatment. There were other endpoints relating to HbA1c and blood glucose control.

Sample size calculations were based on the estimation that the change in HbA1c from baseline after 24 weeks would be -0.5% for an empagliflozin group (10 mg or 25 mg) compared with placebo, with a SD of 1.1%. This was designed as a superiority study of empagliflozin versus placebo.

Baseline data:-61.3% of the FAS were male; 64.1% were Asian; the mean HbA1c was 7.88% and the mean BMI was 28.15 kg/m^2.

The primary efficacy analysis showed statistically significant greater reduction in HbA1c over placebo with empagliflozin 10 mg (adjusted mean difference from placebo: -0.74%, standard error (SE) 0.07%; 97.5% CI: -0.90, -0.57($p < 0.0001$)), empagliflozin 25 mg (-0.85%, SE 0.07%; 97.5% CI: -1.01, -0.69 ($p < 0.0001$)) and sitagliptin 100 mg (-0.73%, SE 0.07%; 95% CI: -0.88, -0.59). The open label arm was analysed descriptively and the mean change was -3.10% (SE 0.22%).

The secondary efficacy endpoints were similar. Treatment with both empagliflozin 10 mg and 25 mg reduced body weight and BP compared with sitagliptin treatment, although there was no direct statistical comparison between empagliflozin and sitagliptin.

The evaluator comments that both doses of empagliflozin showed statistically significant superiority in terms of the primary efficacy end point and the first two key secondary efficacy endpoints. There was no formal comparison with sitagliptin; however, the reduction in HbA1c was numerically greater with empagliflozin 25 mg.

Study 1245.38 is a Phase IIb, double blind, randomised, parallel group efficacy and safety study of empagliflozin (5 mg, 10 mg, 25 mg, and 50 mg) compared to placebo when administered orally qd over 12 weeks, as monotherapy, in patients with type 2 diabetes and insufficient glycaemic control despite diet and exercise, followed by a 40 week randomised extension study to assess long term safety of empagliflozin (10 mg and 25 mg). 615 patients were entered in the 2 week placebo run-in period and then 547 patients were entered in the 12 week first treatment period.

The majority of the patients were male (75%), all were Japanese with mean age of 57.5 years, mean BMI was 25.47 kg/m^2, mean HbA1c (%) ranged from 7.92 to 8.02 and mean FPG ranged from 154.0 to 158.0 mg/dL. Overall, 33.6% had normal renal function, 65.1% and 1.3% had mild and moderate renal impairment, respectively.

The primary efficacy analysis showed that all empagliflozin doses led to statistically significant reduction in HbA1c compared with placebo. Empagliflozin 5 and 10 mg doses showed similar efficacy; the efficacy of 25 and 50 mg doses was also similar to each other but greater than that of the 5 or 10 mg doses. The higher doses also showed similar efficacy in relation to FPG.

Add-on therapy

With pioglitazone alone or pioglitazone + metformin (Study 1245.19)

This was similar in design to 1245.20; however, the subjects were on pioglitazone or pioglitazone + metformin. The inclusion and exclusion criteria, statistical methods and efficacy variables were broadly similar to the previous study.

In the study, 499 were randomised; 166, 165 and 168 patients were randomised to the placebo, empagliflozin 10 mg and 25 mg groups, respectively.

In relation to ethnicity, 57.8% were Asian; 39.6% were white and the largest proportion of randomised patients was from India (41.1%). 48.4% of all patients were male. Mean age was 54.5 years; 56% had a diagnosis of diabetes for up to 5 years. Mean eGFR (according to Modification of Diet in Renal Disease (MDRD) formula) was 85.74 mL/min/1.73m^2 and most patients had normal renal function (38.2%) or mild renal impairment (51.0%); 10.8% had moderate renal impairment; mean (SD) BMI was 29.2 (5.5) kg/m^2, and baseline

HbA1c was 8.09% (0.88). It is noted that 75.5% were on metformin and pioglitazone; 24.3% were on pioglitazone only. Due to the small number of subjects who had pioglitazone, the evaluator states that the statistical analysis, *"was removed from the hierarchical sequence and only performed as an exploratory analysis ....after the implementation of a protocol amendment"*.

Primary efficacy analysis

Compared with placebo, adjusted mean change from baseline at week 24 in HbA1c was statistically significantly greater for empagliflozin 10 mg (-0.48%; 97.5% CI: -0.69% to -0.27%; $p < 0.0001$) and 25 mg (-0.61%; 97.5% CI:-0.82% to -0.40%; $p < 0.0001$). Both doses of empagliflozin (10 mg and 25 mg) were also superior to placebo in the subpopulation of patients with pioglitazone in combination with metformin background medication.

Secondary efficacy analysis

There were statistically significant reductions compared with placebo in FPG, body weight, SBP and DBP with the two doses of empagliflozin at 24 weeks. Of note, the change in body weight compared with placebo was empagliflozin 10 mg (-23.48; 97.5% CI: -31.81 to -15.15; $p < 0.0001$) and 25 mg (-28.46; 97.5% CI: -36.73 to -20.19; $p < 0.0001$). The higher dose of 25 mg showed numerically greater reduction in HbA1c and FPG than the 10 mg dose (but body weight did not show a dose response). However, there was no statistical comparison between the 2 doses of empagliflozin.

Concomitant administration of metformin or metformin + sulfonylurea: Study 1245.23

This study was similar in design to the previous studies. However, they are presented as 2 substudies, depending on the background medication: metformin or metformin + sulfonylurea.

The main inclusion criteria were T2DM and insufficient glycaemic control (HbA1c ≥ 7.0 and ≤ 10.0%) despite therapy with metformin alone or metformin plus sulfonylurea; age ≥ 18 years; BMI ≤ 45 kg/m^2. Exclusion criteria were as per previous studies.

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean MDG after 24 weeks of treatment.

Results of Substudy A: 1245.23 (metformin)

A total of 638 patients were randomised in a 1:1:1 ratio to receive treatment with empagliflozin 10 mg (217 patients), empagliflozin 25 mg (214 patients) or placebo (207 patients) in addition to their metformin background therapy. At baseline, 44.3% of the patients had normal renal function, 50.2% had mild and 5.5% of patients had moderate renal impairment. Mean baseline HbA1c was similar across the randomised treatment groups (7.9%).

Primary efficacy analysis

The mean change from baseline showed statistically significantly ($p < 0.001$) greater reduction in HbA1c with both empagliflozin doses compared with placebo (-0.13%, -0.70% and -0.71% with placebo, empagliflozin 10 mg and 25 mg, respectively).

The adjusted mean change from baseline in body weight showed statistically significantly greater reduction in both empagliflozin groups (-2.08, -2.46 and -0.45 kg for the empagliflozin 10 mg, 20 mg and placebo groups, respectively). After 24 weeks of treatment, there were clinically relevant and statistically significant reductions in MDG with both doses of empagliflozin (adjusted mean change from baseline in MDG was -9.64, -14.36 and -1.99 mg/dL for empagliflozin 10 mg, 25 mg and placebo groups, respectively).

The evaluator mentions that clinically meaningful reductions in BP were observed at 24 weeks. Among those patients not already at the BP goal at baseline, more patients in the empagliflozin groups (10 mg = 35.9%; 25 mg = 30.4%) reached the BP goal after 24 weeks of treatment, compared with the placebo group (13.2%).

Reductions in waist circumference in the empagliflozin treatment groups were consistent with reduction in body weight after 24 weeks of treatment. Results on rescue medications reflected similar trends.

Results of Substudy B: 1245.23 (metformin + sulfonylurea)

A total of 669 patients were randomised in a 1:1:1 ratio to receive treatment with either empagliflozin 10 mg (226 patients), empagliflozin 25 mg (218 patients) or placebo (225 patients) in addition to their metformin plus sulfonylurea background therapy.

Baseline characteristics in relation to sex, ethnicity, age and BMI were similar to other studies. The mean HbA1c was 8.1%. At baseline, 42.0% of patients had normal renal function, 49.2% had mild renal impairment, and 8.7% had moderate renal impairment.

Primary efficacy endpoint

After 24 weeks of treatment, there were clinically relevant and statistically significant ($p < 0.001$) reductions in HbA1c with both doses of empagliflozin; the adjusted mean change from baseline in HbA1c was -0.82%, -0.77% and -0.17% in the empagliflozin 10 mg, 25 mg and placebo groups, respectively.

Key secondary efficacy endpoint

After 24 weeks of treatment, there were clinically relevant and statistically significant reductions in body weight with both doses of empagliflozin (adjusted mean change from baseline in body weight was -2.16, -2.39 and -0.39 kg in the empagliflozin 10 mg, 25 mg and placebo groups, respectively). After 24 weeks of treatment, there were statistically significant and clinically relevant reductions in MDG with both doses of empagliflozin compared with placebo. The adjusted mean change from baseline in MDG was -10.01 mg/dL for the empagliflozin 10 mg group and -13.06 mg/dL for the empagliflozin 25 mg group, compared with no change in the placebo group. There were statistically significant reductions (compared with placebo) in relation to FPG and SBP.

Add-on to metformin-active comparator (glimepiride) controlled study, 1245.28

This was a Phase III randomised, double blind, active-controlled parallel group efficacy and safety study of empagliflozin 25 mg daily compared to glimepiride (1 to 4 mg) in patients with T2DM and insufficient glycaemic control despite metformin treatment. This was a 104 week duration study with a 104 week extension period in patients with T2DM with insufficient glycaemic control. The study included patients with T2DM and insufficient glycaemic control at screening (HbA1c ≥ 7.0 to ≤ 10.0%) despite therapy with immediate release metformin at the maximum tolerated dose (≥ 1500 mg/day) unchanged for at least the last 12 weeks prior to randomisation; age ≥ 18 years; BMI at screening ≤ 45 kg/m^2. There was an interim study report at 52 weeks.

765 patients were randomised to empagliflozin and 780 to glimepiride. Mean age of 56 years, mean BMI was 25.47 kg/m^2, mean HbA1c (%) ranged from 7.92 to 8.02 (with 76% having HbA1c < 8.5%) and mean FPG ranged from 150 to 158.0 mg/dL. Overall, 41% had normal renal function, 56.8% had mild and 2.8% had moderate renal impairment.

The adjusted mean change in HbA1c from baseline at week 52 was -0.73% and -0.66% for the empagliflozin and glimepiride groups, respectively and non-inferiority between empagliflozin and glimepiride was statistically confirmed. The analyses of all key secondary endpoints showed empagliflozin to be superior to glimepiride (FPG, body weight and SBP).

Other studies

Long term studies: Study 1245.31

This was a Phase III double blind, extension, placebo controlled parallel group safety and efficacy trial of empagliflozin (10 and 25 mg qd) and sitagliptin (100 mg qd) given for minimum 76 weeks (including 24 weeks of preceding trial) as monotherapy or with different background therapies in patients with T2DM previously completing Trial 1245.19, 1245.20 or 1245.23. This study included 1806 patients with T2DM who had successfully completed the preceding blinded studies 1245.19, 1245.20, or 1245.23. No primary efficacy endpoint was defined. Secondary endpoints were the change from baseline in HbA1c, body weight, waist circumference, FPG, and SBP and DBP after a total treatment duration of 52 weeks (24 weeks in the preceding trial plus 28 weeks in the extension).

Overall, treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful improvement of glucose control, weight, and BP in patients with T2DM who were either drug naïve or on a background treatment with pioglitazone, metformin alone, or metformin and sulfonylurea, which was sustained over 52 weeks of treatment.

Add-on with insulin: (Study 1245.33)

This was a Phase II study which was randomised, double blind, placebo controlled, parallel group, safety and efficacy study of empagliflozin (10 mg and 25 mg) administered orally, qd over 78 weeks in T2DM patients receiving treatment with basal insulin (glargine, detemir, or intermediate acting Neutral Protamine Hagedorn (NPH) insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycaemic control.

The study included 498 patients aged > 18 years with T2DM with HbA1c > 7% and ≤ 10.0% and on basal insulin (glargine or detemir insulin of ≥ 20 IU/day or NPH insulin ≥ 14 IU/day) with or without concomitant metformin and/or sulfonylurea therapy; the subjects were randomised on 1:1: 1 to receive empagliflozin or placebo. The primary endpoint of change from baseline in HbA1c at 18 weeks showed statistically significantly ($p < 0.001$) greater reduction in both empagliflozin groups compared with placebo; the adjusted mean differences versus placebo were -0.56% (97.5%CI: -0.78, -0.33) and -0.70% (97.5% CI: -0.93, -0.47) in the empagliflozin 10 and 25 mg groups, respectively. The second part of the study (after week 18) examined key secondary endpoints. The key secondary endpoints analysed at 78 weeks were intended to show decreased use of insulin (difference) accompanied by similar levels of HbA1c (non-inferiority) or even greater decrease in HbA1c (difference) compared with placebo. The adjusted mean differences from placebo at week 78 were -6.66 IU in the empagliflozin 10 mg group (97.5% CI: -11.56, -1.77) and -5.92 IU in the empagliflozin 25 mg group (97.5% CI: -11.00, -0.85). As insulin background dose could be adjusted after week 18 to meet an FPG of < 110 mg/dL, insulin sparing was achieved along with the reductions in HbA1c at week 78.

Study 1245.36: Renal impairment patients.

This was a Phase III, randomised, double blind, placebo controlled, parallel group study of empagliflozin treatment (10 mg and 25 mg, qd) compared to placebo treatment as add-on to pre-existing antidiabetic therapy in patients with T2DM with insufficient glycaemic control and different degrees of renal impairment over 52 weeks. The main inclusion criteria T2DM and insufficient glycaemic control (HbA1c ≥ 7.0 and ≤ 10.0%) despite antidiabetic therapy and renal impairment with eGFR between 15 and < 90 mL/min/1.73m^2; age ≥ 18; BMI ≤ 45 kg/m^2. Randomisation was stratified by HbA1c, renal function, and background medication at screening. Statistical calculations for sample size are considered and are acceptable.

A total of 741 patients were randomised based on their renal function at screening. Overall, 292 patients with mild renal impairment were randomised in a 1:1:1 ratio (97, 98 and 97 to empagliflozin 10 mg, 25mg and placebo, respectively), 375 patients with moderate renal impairment were randomised in a 1:1 ratio to either placebo (187 patients) or empagliflozin 25 mg (188 patients) and 74 patients with severe renal impairment were randomised in a 1:1 ratio to either placebo (37 patients) or empagliflozin 25 mg (37 patients) treatment. In addition, a combined set of patients with mild or moderate renal impairment was defined for analysis, which comprised 282 and 284 patients treated with placebo and empagliflozin 25 mg, respectively. Majority of the patients had been diagnosed with diabetes for more than 10 years (61.5%). The demographic and most baseline characteristics were well balanced across the treatment groups for the overall patient population.

Superiority of empagliflozin 25 mg over placebo was demonstrated for the change of HbA1c after 24 weeks of treatment for patients with mild renal impairment, moderate renal impairment, and for the combined set of patients with mild or moderate renal impairment. Similar improvements in HbA1c were observed with empagliflozin compared with placebo at 52 weeks. In patients with mild or moderate renal impairment, empagliflozin produced greater reduction in FPG compared with placebo at 24 and 52 weeks. The results of the primary endpoint were supported by clinically meaningful and consistent reductions in FPG, body weight and BP for empagliflozin treatment.

Study 1245.48: Hypertensive patients

This was a Phase III randomised, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of empagliflozin 10 mg, 25 mg administered orally, qd over 12 weeks in hypertensive patients with T2DM. These patients (in addition to inclusion criteria stated in previous studies) also had hypertension (SBP of 130 to 159 mmHg and DBP of 80 to 99 mmHg).The primary endpoint was the change from baseline in HbA1c after 12 weeks of treatment. The co-primary endpoint was the change from baseline in mean 24 h SBP after 12 weeks of treatment. The key secondary endpoint was the change from baseline in mean 24 h DBP after 12 weeks of treatment. 825 were entered and 824 were treated. The adjusted mean change from baseline in HbA1c was statistically significantly greater for both empagliflozin groups compared with placebo. After 12 weeks of treatment, there were statistically significant and clinically meaningful reductions with both doses of empagliflozin in mean 24 h SBP (adjusted mean change from baseline was -2.99, -3.59 and +0.42 mmHg, respectively) and mean 24 h DBP (the adjusted mean change from baseline in mean 24 h DBP was -1.10, -1.32 and + 0.30 mmHg, respectively).

Uncontrolled long term Study 1245.24

This was an open label, Phase IIb, 78 week extension trial of the blinded 12 week dose finding studies 1245.9 and 1245.10. The clinical evaluator mentions that "The efficacy of empagliflozin in terms of reduction of HbA1c, FPG, body weight, and waist circumference was generally maintained over 90 weeks, adding the preceding studies (12 weeks) and the extension (78 weeks) together. Taken together, long term treatment with empagliflozin demonstrated sustained glycaemic control and weight loss while being well tolerated."

The meta-analysis of the pivotal studies confirmed the finding of the individual pivotal studies.

Overall efficacy

The clinical evaluator states that the 4 pivotal studies demonstrated superiority of empagliflozin over placebo for both doses, 10 and 25 mg. 25 mg showed numerically larger effect in relation to the reduction of HbA1c and in relation to the percentage responders of HbA1c less than 7. Empagliflozin improved glycaemic control as monotherapy and as add-on to metformin monotherapy, metformin plus sulfonylurea, and pioglitazone (with or without metformin). Almost maximal efficacy of empagliflozin on

glycaemic control was established already 12 weeks after the start of treatment. Efficacy was sustained for at least 52 weeks, as shown in the double blind extensions of the 4 pivotal trials.

Empagliflozin also provided significant and clinically meaningful reductions in HbA1c compared with placebo in all other Phase III placebo controlled trials, that is, in patients treated with basal insulin, in patients with T2DM and hypertension, in patients with mild and moderate renal impairment, and in patients with increased cardiovascular risk (including a subpopulation of patients with increased cardiovascular risk on a background of metformin and DPP-4 inhibitor, with or without 1 additional oral antidiabetic agent).

Empagliflozin treatment led to statistically significant and clinically meaningful reductions in body weight in all pivotal trials. Furthermore, significant and clinically meaningful reductions of SBP compared with placebo were achieved for empagliflozin 25 mg in each of the pivotal trials. For DBP, reductions were also observed but were smaller and not always significant compared with placebo.

For body weight, mean changes relative to placebo after 52 weeks across the studies were statistically significant and ranged from -1.58 to -2.07 kg in the empagliflozin 10 mg group and from -1.83 to -2.19 kg in the empagliflozin 25 mg group.

Safety

A total of 13183 patients with T2DM were treated in the clinical studies; of these, 3311 patients were treated with empagliflozin 10 mg, 4563 were treated with empagliflozin 25 mg, and 4697 were treated with comparator medications (placebo, metformin, sitagliptin and glimepiride).

In the studies conducted on patients with diabetes, 63% were males; 65% had diabetes for more than 5 years. The frequencies of treatment-emergent AEs in the empagliflozin groups (68.1% for 10 mg and 69.5% for 25 mg) were similar to the placebo group (68.6%). The most often reported events were hypoglycaemia, hyperglycaemia, nasopharyngitis, and UTI. Apart from hyperglycaemia, the rest were evenly reported in the empagliflozin and placebo groups. The frequencies of patients with AEs assessed by the investigator as drug related were higher in the empagliflozin groups (20.6% for 10 mg and 19.9% for 25 mg) than in the placebo group (15.2%). Genital infections were reported as drug related AEs more frequently in the empagliflozin groups than in the placebo group.

The discontinuation rates due to AEs were similar for all groups (4.8% for empagliflozin 10 mg, 4.9% for empagliflozin 25 mg, and 5.3% for placebo). UTI was reported for higher proportions of patients in the empagliflozin groups than in the placebo group.

SAEs (including fatal events) were lower in the empagliflozin groups (9.6% for 10 mg and 10.3% for 25 mg) than in the placebo group (12.7%). Cardiac disorders were reported as SAEs with lower frequencies in the empagliflozin groups (2.1% for 10 mg and 2.3% for 25 mg) than in the placebo group (4.0%). The incidence rate per 100 patient-years of patients with fatal AEs was lower with empagliflozin treatment (0.52; 41 deaths; including all doses) than with comparator treatments (0.78; 33 deaths; including placebo).

There were more patients with liver enzyme elevation (ALT/AST ≥ 3x ULN with total bilirubin ≥ 2x ULN or ALT/AST ≥ 10x ULN) in the empagliflozin groups (11 patients) than in the comparator groups (1 patient).

Effects on renal function were in general similar for all groups, based on the evaluation of renal AEs and laboratory parameters. The changes in eGFR were considered to be clinically of minimum significance.

There were small increases in haematocrit values. These increases were reversible on discontinuation of empagliflozin. The frequencies of patients with thromboembolic

adverse events did not increase with empagliflozin treatment (0.08% for 10 mg and 0.09% for 25 mg; 0.23% for placebo).

Empagliflozin treatment led to small dose dependent increases (around 0.1 mmol/L) in total cholesterol, HDL cholesterol, and LDL cholesterol but no change in LDL/HDL cholesterol ratio.

Cardiovascular safety: An interim meta-analysis on randomised, double blind Phase II or III studies (of minimum duration 12 weeks) is discussed. The primary endpoint was the 4-point MACE composite endpoint.

Overall conclusions of the clinical evaluator

Benefits relate to efficacy in treatment naïve subjects, add-on to metformin, metformin + sulfonylurea and add-on to basal insulins. Empagliflozin was shown to be non-inferior to sitagliptin and glimepiride in terms of efficacy. Efficacy was seen in (mild and moderate) renal impairment, hypertension and in those with CV risk factors. Efficacy was maintained up to 52 weeks. Empagliflozin has an acceptable safety profile. The issues identified were: efficacy was not shown in those with moderate renal impairment (Grade 3B with EGFR < 45 mL/kg/m^2) and severe renal impairment. The evaluator recommends that renal function be monitored regularly as efficacy is dependent on renal function. Genital infections, increased urination, UTIs, hypoglycaemia, and volume depletion were identified as listed side effects. Efficacy was not established with pioglitazone.

Overall, the evaluator considered the risk benefit is acceptable.

Some questions were raised by the evaluator. They are discussed in the CER (see Attachment 2 of this AusPAR). It was noted that the sponsor agreed to modify the proposed *Indications* as recommended by the evaluator.

Clinical evaluator's recommendation

The clinical evaluator recommended that empagliflozin be approved for the following, modified, indication:

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.*
>
> *Add-on combination therapy: In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials).*

Risk management plan

No advice from the Advisory Committee on the Safety of Medicines (ACSOM) was requested. The sponsor proposes routine risk minimisation activities: the evaluator considers this unacceptable and recommends amendments relation to the *Precautions*, *Adverse Events* section of the PI. An educational programme acceptable to the TGA is recommended as a condition of registration. All draft education materials, a clear distribution plan and measures to address effective were also recommended to be provided to the TGA.

Risk-benefit analysis

Delegate's considerations

Lack of absolute bioavailability study: The sponsor's justification for not submitting an absolute bioavailability study has been accepted by the chemistry and clinical evaluators. The justification essentially rests on the fact that dissolution is unlikely to be a rate limiting step. In addition, it is stated that, *"the within subject and inter-subject variability was low considering the wide demographic range evaluated in long term clinical studies. There were no clinically relevant changes in empagliflozin exposure that could be attributed to any of the intrinsic or extrinsic factors evaluated in the extensive pharmacology assessment"*. Be that as it may, this is a new chemical entity which requires an absolute bioavailability to fully characterise the PK of the product. Other products for this class, dapagliflozin and canagliflozin included absolute bioavailability studies in the data package. It is recommended that bioavailability relative to a suitable oral solution be conducted especially as it is soluble in water, as a condition of registration. In relation to the current draft PI, there should be a statement in the *Pharmacology* section that there is no absolute bioavailability study conducted with empagliflozin. This submission has not been considered by PSC.

Efficacy studies have shown clinically useful reductions in HbA1c. Efficacy is dependent on renal function and therefore will be less effective in older patients and those whose renal function is severely impaired. Subgroup analysis revealed that in those with moderate renal impairment (Stage 3B), there were no significant changes in relation to the efficacy endpoints.

The sponsor has not included severe renal impairment as a Contraindication. This is included in the *Precautions* as Jardiance is not recommended for use in patients with eGFR < 45 mL/min/1.73 m^2.

Monotherapy is supported by one pivotal study where the comparators were placebo and sitagliptin; this was conducted in treatment naïve patients. (Sitagliptin is currently registered for monotherapy in T2DM). The reduction in HbA1c with empagliflozin 10 mg was similar to that observed with sitagliptin 100 mg, though no direct statistical comparison is made. Empagliflozin 25 mg showed an increase that was numerically greater. There was statistically significant weight reduction and SPB reduction in comparison with placebo with empagliflozin; this was sustained over 52 weeks.

Add-on to metformin and add-on to metformin and sulfonylurea are supported by the efficacy findings in Study 1245.23. The primary efficacy endpoint was HbA1c and secondary endpoints bodyweight and SBP. The efficacy appeared to be sustained at 52 weeks.

There is also a pivotal efficacy study supporting the use of empagliflozin with metformin + pioglitazone (1245.19). However, this study only included a small number of subjects on empagliflozin+ pioglitazone and thus, does not support dual therapy with pioglitazone. This should be specified clearly in the table describing the study in the draft PI: that is, the number of subjects using pioglitazone (+ empagliflozin) should be specified; it also should be stated that there was no formal statistical analysis of efficacy in this group.

Add-on to insulin is only supported by one Phase II study (1245.33). It is usual to have several Phase III studies to support use with basal insulins. It is noted, however, that the other products in this class have one pivotal study that supported registration. This study showed a statistically significant difference of HbA1c at 18 weeks and an insulin sparing effect was observed when followed up for 78 weeks. Description of this study is included in the draft PI; this should include some relevant baseline characteristics (such as the duration of diabetes, concomitant antidiabetic medications, and age of the patient).

There was a study in hypertensive patients that showed statistical and clinically significant reduction in SBP and DBP. The pivotal efficacy studies showed statistically significant reduction in SBP compared with placebo. DBP reductions were smaller but not always significant compared with placebo. These reductions may be the result of diuresis observed with this class of drugs.

As with the other drugs of this class, modest weight reduction is observed in the monotherapy studies and add-on studies (metformin, sulfonylurea and others). The reduction in weight in the study with insulin appeared not to be sustained at week 78. Weight reduction is unlikely to be seen with pioglitazone; this could not be assessed in the study with pioglitazone because of the small numbers involved.

The combined use of empagliflozin with GLP-1 analogues has not been studied; however, the additive effects on weight loss might be of potential concern. It is recommended that the PI include a cautionary statement till clinical trial data are available on combined use.

The established risks were genital infections, polyuria and hypoglycaemia.

An interim meta-analysis on randomised, double blind Phase II or III studies does not suggest a cardiac safety concern with empagliflozin. The applicant is also conducting a long term CV outcome study (1245.25), which is placebo controlled and includes patients with type 2 diabetes and high CV risk. This is relevant as the efficacy studies were conducted on those with stable heart disease.

Proposed action

Overall the Delegate accepts that the risk benefit ratio is favourable and proposed to approve Jardiance empagliflozin 10 mg and 25 mg film coated tablets for:

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control for patients in whom use of metformin is considered inappropriate due to intolerance.*
>
> *Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials).*

Proposed conditions of registration

- A bioavailability study relative to a suitable oral solution be conducted;
- An educational programme acceptable to the TGA as recommended by the RMP evaluator;
- Finalisation of the PI to the satisfaction of the TGA[28].

Request for ACPM advice

The Delegate proposed to seek advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. Does the Committee accept that efficacy and safety are adequate to register add-on treatment with insulin with the details of the available data in the *Clinical trials* section?

[28] Details of proposed revisions to the PI are beyond the scope of the AusPAR

2. Does the Committee agree with the Delegate that severe renal impairment should be a Contraindication as per the other registered drugs of this class?
3. Does the Committee agree that the lack of absolute bioavailability should be included in the draft PI; and that a relative bioavailability study should be conducted as a condition of registration?
4. Does the Committee agree with the evaluator and the sponsor that the starting dose be 10 mg /day and increased to 25 mg/day in view of the fact that the pivotal studies have not used this regimen?
5. Does the Committee agree that the risk benefit profile is adequate and the product can be registered for the requested indications?

Response from sponsor

Boehringer Ingelheim Pty Limited (BI) supports the Delegate's recommendation for the registration of Jardiance empagliflozin (10 mg and 25 mg) film coated tablets for the following indications:

> *"Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control for patients in whom use of metformin is considered inappropriate due to intolerance.*
>
> *Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials)."*

BI comments to the issues raised by the TGA delegate in the delegate's overview

Delegate's question to ACPM: Does the Committee agree that the risk benefit profile is adequate and the product can be registered for the requested indications?

BI believes that a positive risk to benefit ratio has been demonstrated for both doses (10 mg and 25 mg) of empagliflozin (Jardiance) for the above mentioned indications.

Empagliflozin (10 mg and 25 mg) has consistently demonstrated sustained, clinically meaningful, and statistically significant efficacy. Also both doses were well tolerated and there were no meaningful differences between the overall safety profiles. In regard to the frequency of any AE, severe AEs, serious AEs, AEs leading to treatment discontinuation, or fatal AE, similar proportions of patients were noted with such events for both doses.

Delegate's question to ACPM Does the Committee accept that efficacy and safety are adequate to register add on treatment with insulin with the details of the available data in Clinical trials section?

As commented by the Delegate, *"other products in this class have one pivotal study that supported registration"*. BI believes that Study 1245.33 is an adequate and well controlled study which provided sufficient efficacy and safety data to support the registration of add-on treatment with insulin. In the draft PI, BI has included within the *Clinical trial* section, data after 18 and 78 weeks of treatment. This is in contrast to the other registered products in this class, where the data supporting add-on treatment with insulin are: 18 weeks for canagliflozin, or 24 and 48 weeks for dapagliflozin. Therefore, BI asserts that the efficacy and safety are adequate to register add on treatment with insulin."

Delegate's question to ACPM: Does the Committee agree with the delegate that severe renal impairment should be a contraindication as per the other registered drugs of this class?

BI agrees to include the warning of patient with severe renal impairment as a contraindication.

Delegate's question to ACPM: Does the Committee agree with the evaluator and the sponsor that the starting dose be 10 mg/day and increased to 25 mg/day in view of the fact that the pivotal studies have not used this regimen?

BI acknowledges that the proposed starting dose of 10 mg/day and increase to 25 mg/day was not the regimen used in the pivotal studies. The proposed approach represents a simple dosing recommendation which is consistent with the other SGLT2 inhibitor, canagliflozin.

As highlighted in the CER *"The modified dosing regimen ensures that the lowest effective dose is used in patients".* BI has demonstrated the positive risk to benefit ratio for both doses of empagliflozin for the proposed indications. Since, empagliflozin 10 mg provides substantial efficacy with lower exposure, 10 mg is recommended as a starting dose. On the other hand, the clinical findings show that, on average, empagliflozin 25 mg promotes better HbA1c reduction than empagliflozin 10 mg. This is also reflected by the higher proportion of patients who reached the HbA1c target of < 7% with empagliflozin 25 mg (37.2%) than with empagliflozin 10 mg (31.5%) in the pooled pivotal trials at 24 weeks. Additionally, a lower proportion of patients in the 25 mg dose group (2.4%) than in the 10 mg group (4.1%) required rescue medication in the pooled pivotal trials. When taken together, the data support that for patients tolerating 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily.

Delegate's question to ACPM: Does the Committee agree that the lack of absolute bioavailability should be included in the draft PI [and that] a relative bioavailability study should be conducted as a condition of registration.

BI does not support the proposal that a relative bioavailability study should be conducted as a condition of registration. In our application, BI provided a justification for not performing an absolute bioavailability study. As noted by the Delegate, *'The sponsor's justification for not submitting an absolute bioavailability study has been accepted by the chemistry and clinical evaluators*'. However, the Delegate insists that *'Be that as it may, this is a new chemical entity which requires an absolute bioavailability for fully characterise the PK of the product'* and *'It is recommended that bioavailability relative to a suitable oral solution be conducted especially as it is soluble in water…'.* The Delegate's argument is that the PK of empagliflozin cannot be fully characterised unless an absolute bioavailability study is conducted.

Empagliflozin is highly soluble, based on the Biopharmaceutics Classification System (BCS) classification, and dissolution is not considered to be rate limiting for its absorption. Although permeability could be a rate limiting factor, empagliflozin demonstrated linear PK over the dose range 0.5 to 800 mg after single doses and 2.5 to 100 mg after multiple doses in humans. The within subject and inter-subject variability was low considering the wide demographic range evaluated in long-term clinical trials. There were no clinically relevant changes in empagliflozin exposure that could be attributed to any of the intrinsic and extrinsic factors evaluated in the extensive clinical pharmacology assessment. Based on these robust data, empagliflozin exposure is not expected to fluctuate beyond the range evaluated in the target population to an extent that may lead to any safety related concerns.

The data suggest that empagliflozin is well tolerated and there were no exposure dependent safety related concerns over the entire dose range evaluated in clinical trials. The highest doses evaluated in clinical trials were 800 mg (single doses) and 100 mg (multiple doses) which were 32- and 4-fold higher than the proposed highest therapeutic dose (25 mg once daily), respectively. Hence, any further increases in empagliflozin

exposure, due to any unknown factors, should still be within the wide safety window established in the extensive clinical program.

As such, the sponsor's position is that the lack of absolute bioavailability data or relative bioavailability versus an oral drinking solution for empagliflozin tablets is not a concern, and that further evaluation does not add to the robust PK data already generated for this product.

BI comments on additional issues raised in the CER

BI provides the following response to the recommendation made by the clinical evaluator in their report that *'as a precautionary measure, empagliflozin should not be recommended for use in patients concomitantly treated with pioglitazone (similar to PI for dapagliflozin)'*. The clinical evaluator's recommendation was based on: 1) the contrasting results from two PK drug interactions studies between empagliflozin and pioglitazone and 2) epidemiological data for pioglitazone suggesting a small increase risk of bladder cancer in diabetic patients. It is important to note that unlike dapagliflozin, no imbalance in bladder cancer was observed for empagliflozin.

Empagliflozin drug-drug interaction with pioglitazone

Two studies investigated the effect of empagliflozin on the PK of pioglitazone and its active metabolites and the effect of pioglitazone on the PK of empagliflozin following co-administration in healthy volunteers (Trial 1245.17 (U10-2151) and Trial 1245.50 (U11-1194)). In the 1245.17 study, the effect of co-administration of empagliflozin and pioglitazone was investigated with the highest dose of empagliflozin under investigation in Phase IIb dose-finding studies (50 mg) and the highest marketed dose of pioglitazone (45 mg). The 1245.50 study was carried out with the doses of empagliflozin under investigation in Phase III trials (10 mg and 25 mg). The 50 mg empagliflozin dose was added for continuity with the first study. A slight increase in pioglitazone exposure was observed in the 1245.17 study, whereas pioglitazone exposure decreased marginally in the 1245.50 study when pioglitazone was co-administered with empagliflozin compared with pioglitazone alone. The changes observed in pioglitazone exposure in both studies were not considered clinically relevant.

Pioglitazone is available in multiple dose strengths (15 mg, 30 mg and 45 mg for qd administration) and incremental dose titration is recommended for patients not responding to monotherapy (Actos (pioglitazone hydrochloride) Australian PI), suggesting that there may be some variability in exposure over this dose range. Studies of other agents given in combination with pioglitazone have also noted changes in the PK of pioglitazone, which were not considered to warrant dose adjustment. For example, exposure of a single 15 mg dose of pioglitazone increased more than 3 fold when co-administered with the fibrate gemfibrozil[29]; no dose adjustment of pioglitazone is recommended when it is co-administered with gemfibrozil (Actos Australian PI). In a drug-drug interaction study with dapagliflozin and pioglitazone, the lower limit of the 90% CI for GMR of pioglitazone Cmax with or without dapagliflozin was outside the no-effect interval, and the authors concluded that dapagliflozin could be co-administered with pioglitazone without dose adjustment[30].

Interaction between empagliflozin and pioglitazone would not be expected given that empagliflozin does not inhibit, inactivate, or induce the major CYP450 isozymes, the main pathway of pioglitazone metabolism (U07-3480, U10-3595): reports provided in the

[29] Jaakkola T, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. *Clin Pharmacol Ther* 2005;77:404-414.
[30] Kasichayanula S et. al. Lack of pharmacokinetic interaction between dapagliflozin, a novel sodium-glucose transporter 2 inhibitor, and metformin, pioglitazone, glimepiride or sitagliptin in healthy subjects. *Diabetes Obes Metab* 2011;13:47-54.

dossier, which are the main mechanisms known to cause drug-drug interactions with pioglitazone[31]. In conclusion, these results suggest that there is no clinically relevant drug-drug interaction between empagliflozin (doses administered in Phase III studies) and pioglitazone, and that no dosage adjustment is warranted when these drugs are given concomitantly.

Clinical efficacy and safety of empagliflozin as add-on to pioglitazone

In the pivotal efficacy Study 1245.19, at least 40 patients per treatment arm on the background medication of pioglitazone alone were included. The reduction in HbA1c was statistically significant on the nominal 5% level. The treatment effect was consistent with that observed for patients on the background of pioglitazone + metformin and also for patients using different background medications in the other efficacy studies. Therefore, the efficacy analysis did not suggest any difference between patients receiving pioglitazone alone or other anti-diabetic background medications (see Table 12 below).

Table 12: HbA1c (%) change from baseline ANCOVA results at Week 24 by background medication- FAS (LOCF)

	Placebo	Empagliflozin	
		10 mg	25 mg
All patients in study 1245.19, N	165	165	168
Adjusted[1] mean (SE)	−0.11 (0.07)	−0.59 (0.07)	−0.72 (0.07)
Difference to placebo (SE)	--	−0.48 (0.09)	−0.61 (0.09)
95.0 % confidence interval	--	−0.69, −0.27	−0.82, −0.40
p-value	--	<0.0001	<0.0001
Pioglitazone alone, N	41	40	41
Adjusted[2] mean (SE)	−0.14 (0.13)	−0.70 (0.14)	−0.78 (0.13)
Difference to placebo (SE)	--	−0.56 (0.19)	−0.64 (0.19)
95.0 % confidence interval	--	−0.94, −0.19	−1.01, −0.27
p-value	--	0.0034	0.0008
Pioglitazone+metformin, N	124	125	127
Adjusted[2] mean (SE)	−0.10 (0.08)	−0.55 (0.08)	−0.69 (0.08)
Difference to placebo (SE)	--	−0.45 (0.11)	−0.60 (0.11)
95.0 % confidence interval	--	−0.67, −0.24	−0.81, −0.38
p-value	--	<0.0001	<0.0001

SE= standard error

[1] Model included baseline HbA_{1c} ($p<0.0001$) as a linear covariate, baseline eGFR (MDRD) ($p=0.5105$), treatment ($p<0.0001$), baseline background medication ($p=0.2957$) as fixed effects

[2] Model included baseline HbA_{1c} ($p<0.0001$) as a linear covariate, baseline eGFR (MDRD) ($p=0.5180$), treatment ($p<0.0001$), baseline background medication ($p=0.2952$), and treatment by baseline background medication interaction ($p=0.8821$) as fixed effects

The empagliflozin PI includes information based on a large development program (around 13000 patients in total) and specific to the drug and its proposed indication. The pooled analysis on malignancy did not show an increase in bladder cancer with empagliflozin treatment. In the pivotal Study 1245.19 and its long term safety extension (1245.31; mean exposure 88 weeks to empagliflozin 10 mg or 25 mg on the background of pioglitazone ± metformin), no bladder cancer AE was reported. Based on these data, there is currently no evidence for a potential increased risk of bladder cancer.

In summary, the changes observed in pioglitazone exposure with empagliflozin 50 mg in Study 1245.17 are considered not to be clinically significant; and in Study 1245.50, when the recommended empagliflozin doses in the PI (10 mg and 25 mg) were administered,

[31] Jaakkola T, Laitila J, Neuvonen PJ, Backman JT. Pioglitazone is metabolised by CYP2C8 and CYP3A4 in vitro: potential for interactions with CYP2C8 inhibitors. *Basic Clin Pharmacol Toxicol* 2006;99:44-51.

pioglitazone exposure even slightly decreased, indicating that the combination is unlikely to increase pioglitazone exposure. Treatment with empagliflozin 10 mg and 25 mg once daily when added to pioglitazone in patients with uncontrolled type 2 diabetes provided statistically significant and clinically meaningful reductions in HbA1c. No added risk of bladder cancer was reported in patients treated for 88 weeks and no major imbalance was observed in other safety parameters. As a result, the sponsor is of the opinion that the benefit risk ratio is positive for empagliflozin in patients concomitantly treated with pioglitazone."

Changes to PI

Details of the sponsor's comments on PI revisions are beyond the scope of the AusPAR.

Conclusion

Boehringer Ingelheim Pty Limited supports the Delegate's recommendation for the registration of the new chemical entity product empagliflozin (Jardiance film coated tablets) for the following indications:

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control for patients in whom use of metformin is considered inappropriate due to intolerance.*
>
> *Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials)."*

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, agreed with the delegate and considered Jardiance film coated tablets containing 10 mg and 25 mg of empagliflozin to have an overall positive benefit-risk profile for the indication;

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> > *Monotherapy: When diet and exercise alone do not provide adequate glycaemic control for patients in whom use of metformin is considered inappropriate due to intolerance.*
> >
> > *Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials).*

Proposed conditions of registration

The ACPM proposed the following conditions of registration:

- Subject to satisfactory implementation of the RMP most recently negotiated by the TGA;
- Negotiation of PI and CMI to the satisfaction of the TGA;

- The draft education materials, a clear distribution plan and measures to address effectiveness were also recommended to be assessed by the TGA.

Proposed PI/CMI amendments

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

Specific advice

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

1. Does the Committee accept that efficacy and safety are adequate to register add on treatment with insulin with the details of the available data in *Clinical trials* section?

The ACPM agreed with the Delegate and clinical evaluator that overall, empagliflozin was safe and efficacious in patients with type 2 diabetes as monotherapy and in combination with other oral antidiabetic medications or insulin.

2. Does the Committee agree with the delegate that severe renal impairment should be a Contraindication as per the other registered drugs of this class?

The ACPM agreed with the Delegate that severe renal impairment should be a contraindication and noted this had been agreed to by the sponsor.

3. Does the Committee agree that the lack of absolute bioavailability should be included in the draft PI? A relative bioavailability study should be conducted as a condition of registration.

The ACPM agreed that while an absolute bioavailability study is always useful, especially for drug characterisation and clinical development, the justification provided by the sponsor seems reasonable and at this point the clinical evidence supports this.

4. Does the Committee agree with the evaluator and the sponsor that the starting dose be 10 mg/day and increased to 25 mg/day in view of the fact that the pivotal studies has not used this regimen?

The ACPM advised that, although empagliflozin 25 mg generally showed numerically better efficacy results than empagliflozin 10 mg, both doses showed a good safety profile. As the regimen proposed was conservative, the lower dose may provide adequate control in some patients.

5. Does the Committee agree that the benefit-risk profile is adequate and the product can be registered for the requested indications?

Empagliflozin demonstrated a favourable safety profile in a very large set of patients with type 2 diabetes using a variety of antidiabetic background medications, including insulin. The ACPM was of the view that the overall benefit-risk profile for empagliflozin 10 mg and 25 mg daily for the proposed indications is favourable.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Jardiance film coated tablets blister pack containing empagliflozin 10 or 25 mg, indicated for:

> *Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Clinical Trials).

Specific conditions of registration applying to these goods

- The Empagliflozin Risk Management Plan (RMP) Version 1.1 (U13-1175-02) (in EURMP format) dated 2 October 2013, data lock point (DLP) 31 August 2012 and Australian Specific Annex Version 1.1 (ASA U13-1175-02) dated 20 December 2013, DLP not given), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Jardiance at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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