Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for saxagliptin / dapagliflozin

Proprietary Product Name: Qtern

Sponsor: AstraZeneca Pty Ltd

October 2017

TGA Health Safety Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- 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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
5-OH	5-hydroxy
ACPM	Advisory Committee on Prescription Medicines
ADA	American Diabetes Association
AE	Adverse event
AEoSI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
5-OH	5-hydroxy
AUC(0-T)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUCinf	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase

Abbreviation	Meaning
CLT/F	Apparent oral plasma clearance
Cmax	Maximum observed plasma concentration
CMI	Consumer Medicines Information
CrCl	Creatinine clearance
CSP	Clinical study protocol
CSR	Clinical study report
CV	Cardiovascular
CV	Coefficient of variation
CYP	Cytochrome
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DPP4	Dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GM	Geometric mean

Abbreviation	Meaning
GMR	Geometric mean ratio
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein-cholesterol
ICH	International Conference on Harmonisation
IR	Immediate release
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL-C	Low density lipoprotein-cholesterol
LT	Long-term
MA	Marked abnormality
MDRD	Modification in Diet and Renal Disease
MI	Myocardial infarction
MOA	Mechanism of action
MRHD	Maximum recommended human dose
MTT	Meal tolerance test
NYHA	New York Heart Association
OH	Hydroxy
OL	Open-label
PD	Pharmacodynamic(s)
PE	Physical examination
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PPG	Postprandial glucose
PRMP	Patient Risk Management Plan
PT	Preferred term
SAE	Serious adverse event

Abbreviation	Meaning
SAP	Statistical Analysis Plan
SE	Single entity
SGLT2	Sodium-glucose cotransporter 2
SMQ	Standard MedDRA Query
SOC	System Organ Class
ST	Short-term
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TG	Triglycerides
TZD	Thiazolidinedione
UGT	Uridine diphosphate glucuronosyl transferase
UKPDS	United Kingdom Prospective Diabetes Study Group
ULN	Upper limit of normal
UTI	Urinary tract infection
XR	Extended-release

I. Introduction to product submission

Submission details

Type of submission:	New fixed dose combination
Decision:	Approved
Date of decision:	21 October 2016
Date of entry onto ARTG:	25 October 2016
Active ingredients:	Saxagliptin (as hydrochloride) / dapagliflozin (as propanediol monohydrate)
Product name:	Qtern
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park NSW 2113
Dose form:	Film-coated tablet
Strengths:	Saxagliptin (as hydrochloride) 5 mg Dapagliflozin (as propanediol monohydrate) 10 mg
Container:	Blister pack
Pack sizes:	7, 28
Approved therapeutic use:	Qtern 5/10 is indicated as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.
Route of administration:	Oral
Dosage:	One 5 mg/10 mg tablet taken once daily at any time of the day, with or without food
ARTG number:	255632

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd to register Qtern 5/10 as a new fixed dose combination (FDC) combining two medicines, saxagliptin (as hydrochloride) and dapagliflozin (as propanediol monohydrate), to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM). Saxagliptin (Onglyza) is an inhibitor of dipeptidyl peptidase 4 (DPP4) enzyme, while dapagliflozin is an inhibitor of renal sodium-glucose co-transporter 2 (SGLT2). Both medicines are listed currently on the ARTG: saxagliptin in 2011, and dapagliflozin in 2012. This will be the first FDC for T2DM in Australia that does not include metformin.

Saxagliptin is a potent and reversible inhibitor of DPP4 that increases the levels of endogenous GLP-1 and potentiates its endocrine actions, augmenting prandial insulin secretion, reducing glucagon secretion, and improving the overall pre- and post-prandial glycaemic profile in diabetic patients. Consistent with its mechanism of action, saxagliptin has been shown to produce significant reductions in HBA1c and plasma glucose concentrations while presenting a low risk for hypoglycaemia.

Dapagliflozin is an inhibitor of the sodium-glucose co-transporter (SGLT2) in the kidney and results in the direct and insulin dependent elimination of glucose by inhibiting the renal reabsorption of glucose and promoting its urinary excretion. This increased excretion of glucose results in a reduction of HBA1c and in fasting and post prandial glucose levels in the blood, and in the urinary loss of approximately 280 kcalories/day.

The approved indications for saxagliptin at the time of the current submission for Qtern were:

> ***Add-on combination***
>
> ***Dual Oral Combination Therapy***
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.*
>
> ***Triple Oral Combination Therapy***
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in triple combination with metformin plus a sulfonylurea (SU), when the two agents, with diet and exercise, do not provide adequate glycaemic control.*
>
> ***Combination Therapy with Insulin***
>
> *Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycaemic control as add-on therapy to premixed or basal insulin (with or without metformin) when premixed or basal insulin (with or without metformin) used with diet and exercise, do not provide adequate glycaemic control. ONGLYZA has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short-acting insulin (basal:bolus regimens) and its efficacy in this context has not been established.*
>
> ***Initial combination***
>
> *Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).*

The approved indications in the dapagliflozin PI are:

> ***Monotherapy***
>
> *Forxiga is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.*
>
> ***Initial combination***
>
> *Forxiga is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels).*

Add-on combination

Forxiga is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with other anti-hyperglycaemic agents, when these together with diet and exercise, do not provide adequate glycaemic control (see CLINICAL TRIALS and PRECAUTIONS for available data on different add-on combination therapies).

The proposed indications for the saxagliptin/dapagliflozin PI are:

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

The recommended dose of the saxagliptin/dapagliflozin FDC product is one 5 mg/10 mg tablet taken once daily at any time of the day, with or without food. The tablet is to be swallowed whole.

Regulatory status

At time of submission to TGA, the new FDC had been approved for registration by EMA for the following indication:

Qtern, fixed dose combination of saxagliptin and dapagliflozin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- *to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Qtern do not provide adequate glycaemic control;*
- *when already being treated with the free combination of dapagliflozin and saxagliptin.*

The international regulatory status (approvals) at the time of this submission is listed in Table 1.

Table 1: International regulatory status.

Country	Submission date	Comments
EU	20 Apr 2015	CHMP positive opinion 27 May 2016 Centralised procedure Rapporteur: The Netherlands Co-rapporteur: Belgium

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 PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

Three clinical studies have been conducted as part of the Phase III clinical development program for the proposed combination product. The first of these (# CV181169) assessed the safety and efficacy of the concomitant (dual) addition of saxagliptin and dapagliflozin to the therapy of patients with T2DM with insufficient glycaemic control on metformin monotherapy. The second and third studies assessed the safety and efficacy of the sequential (stepwise) addition of saxagliptin and dapagliflozin to the therapy of T2DM patients on metformin, with the saxagliptin plus dapagliflozin plus metformin treatment group showing the greatest improvement in glycaemic control. The proposed FDC product is therefore suggested to be a convenient oral regimen with the potential to achieve earlier and significant glycaemic control, with an adverse event profile consistent with that for the mono products.

There are no BP/Ph. Eur. or USP monographs for saxagliptin/dapagliflozin tablets, so specifications were set in-house.

Drug substance (active ingredient)

Saxagliptin is already marketed by the same sponsor as 2.5 and 5 mg (Onglyza) tablets, and as saxagliptin/metformin hydrochloride (Kombiglyze XR) film coated tablets. Dapagliflozin is marketed as 10 mg (Forxiga) tablets and as dapagliflozin/metformin hydrochloride (Xigduo XR) film coated tablets. The saxagliptin/dapagliflozin film-coated tablets were developed as 2.5 mg/5 mg, 2.5 mg/10 mg, 5 mg/5 mg, and 5 mg/10 mg strengths; however only the 5 mg/10 mg combination is proposed for registration. Pharmaceutical development of the FDC products relied upon the accumulated development knowledge and commercial manufacturing experience from the mono and FDC products referenced above.

Drug product

The drug product is proposed as light brown to brown, biconvex, round, film coated tablets, with 5/10 printed on one side, and “1122” printed on the other side in blue ink. The tablets contain the active substances as well as standard excipients (microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, silicon dioxide, magnesium stearate, as well as the commercial products Opadry II White, and Opadry II Butterscotch). The product is not scored.

The formulation of the finished product, choice of excipients and manufacturing process appear to have been logically developed and optimised with reference to the physical, chemical and pharmacological properties, the compatibility of the active substance and excipients, the dose form, consistency of finished product, and the intended clinical use of the product.

At the time of submission, results for the long term drug stability trials were only available for a maximum period of 12 months. These trials showed that there was no deterioration of the drug product over that 12 month period, and acceptable results were also obtained for the accelerated stability trial over 6 months. Consequently, the requested shelf life of 24 months, with the conditions of “store below 30°C” and “store in original container” is supported.

Biopharmaceutics

The 90% confidence intervals for the test to reference ratios of Cmax, AUC0-t and AUCinf for saxagliptin and dapagliflozin, for the comparison of the 5 mg saxagliptin + 10 mg dapagliflozin mono tablets (reference) versus 5 mg saxagliptin/10 mg dapagliflozin FDC tablets (test) were all within the acceptance criteria required to conclude bioequivalence (that is, 80-125%). The Tmax values obtained for the test and reference products were very similar for both compounds from both treatments; no significance for the median result for saxagliptin was seen during re-calculation by the evaluator, and no difference was recorded in the Study Report.

The pharmacokinetic parameters used to derive these determinations of bioequivalence were based on sound concentration versus time data for both saxagliptin and dapagliflozin, which were obtained from the use of appropriately validated methods for each compound. Quality control results for both analytes were acceptable during sample analysis.

It can therefore be concluded that the proposed test product is bioequivalent to the 5 mg saxagliptin + 10 mg dapagliflozin reference products by the same sponsor.

Quality summary and conclusions

There are no further significant issues requiring resolution before registration and approval is recommended from a pharmaceutical chemistry perspective.

III. Nonclinical findings

Introduction

Qtern is proposed to be used as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both saxagliptin and dapagliflozin is appropriate.

Pharmacokinetics

Rat

Toxicokinetic data from the combination toxicity study (Study DN12107; rat; 3 months) were presented. No notable or consistent pharmacokinetic interaction was evident with co-administration of the two agents.

Human

Saxagliptin (5 mg PO) was reported to have no effect on the pharmacokinetics of dapagliflozin (10 mg PO), and vice versa, in a single-dose study conducted in heathy human subjects (Clinical Study CV181191). Bioequivalence between the FDC tablet and co-administration of individual saxagliptin and dapagliflozin tablets (at 5/10 mg) was additionally reported (Clinical Study CV181341).

Human AUC0-t values of 73 ng·h/mL for saxagliptin and 203 ng·h/mL for BMS-510849 (Clinical Study CV181037), and 438 ng·h/mL for dapagliflozin (Clinical Study MB102027), for administration of 5 mg saxagliptin and 10 mg dapagliflozin, were cited in the nonclinical evaluation reports for the original registration of saxagliptin and dapagliflozin as new chemical entities. These values were used to calculate animal:human exposure

ratios previously. Associated plasma Cmax values for saxagliptin, BMS-510849 and dapagliflozin were 24, 47 and 136 ng/mL, respectively.

Enzyme inhibition

Saxagliptin and BMS-510849 (tested individually up to 50 μM) did not inhibit the conversion of dapagliflozin to dapagliflozin-3O-glucuronide or propofol to propofol-O-glucuronide by human liver microsomes: reactions catalysed by UGT1A9 (Study 930059456). Assay sensitivity was demonstrated using the known UGT1A9 inhibitor, niflumic acid, which inhibited the glucuronidation of dapagliflozin and propofol with IC50 values of 0.2 μM and 0.42 μM for the respective substrates.

Toxicology

There were no treatment related histopathological findings and no notable increase in the severity of other findings with the combination compared with either agent alone other than for urinary protein excretion in males. The sponsor claimed comparability between the combination and the single agent dapagliflozin group, noting the high variability of the parameter; the difference between the two groups was statistically significant, however, and with two values in combination animals exceeding the highest seen in animals treated with dapagliflozin alone (by 14-32%). In the absence of renal microscopic changes, the finding is not considered to be adverse.

Nonclinical summary and conclusions

- The nonclinical submission was of high quality and adequate scope (consistent with the relevant EU guideline)[1]. The nonclinical dossier contained data on pharmacokinetic drug interactions and general toxicity.
- No nonclinical efficacy studies were submitted.
- Saxagliptin is chiefly metabolised by CYP3A4/5. Dapagliflozin was found to have no relevant CYP inhibitory activity in previously evaluated nonclinical studies (tested up to 45 μM; ~1500 times the peak free plasma concentration expected in patients), indicating no impact on the metabolism of saxagliptin with co-administration.
- Dapagliflozin is mainly cleared via metabolism by UGT1A9. Saxagliptin and its major metabolite (BMS-510849; monohydroxylated; pharmacologically active) were shown to not inhibit UGT1A9 in a newly submitted study conducted with human liver microsomes in vitro. The maximum tested concentration (50 μM for each) is equivalent to ~370-650 times the peak free plasma concentration expected in patients. Accordingly, no inhibition of UGT1A9 (which would act to increase exposure to dapagliflozin) is expected in patients receiving saxagliptin.
- In vivo, no notable pharmacokinetic interaction was observed between saxagliptin and dapagliflozin with co-administration by the oral route in rats. Similarly, it was reported that no pharmacokinetic interaction occurs in human subjects.
- A repeat-dose toxicity study of 3 months duration was conducted with the combination in rats. The study was conducted appropriately, and with adequate multiples of the clinical exposure obtained: 2.7 (males) and 7 (females) for saxagliptin; and 6 (males) and 7 (females) for dapagliflozin [as animal:human plasma AUC0-24 h].

[1] European Medicines Agency, "Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005)", 24 January 2008.

Treatment with saxagliptin and dapagliflozin in combination produced no novel or notable exacerbated toxicity cf. the monotherapies.

- The Pregnancy Category proposed by the sponsor (Category D)[2] is considered appropriate, being consistent with the existing categorisation of the single agents (Category B3[3] for saxagliptin and Category D for dapagliflozin).
- The nonclinical safety specification detailed in the sponsor's draft RMP is considered to be acceptable.
- There are no objections on nonclinical grounds to the registration of Qtern.

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

Clinical rationale

Saxagliptin inhibits the DPP4 enzyme. This inhibition leads to slowing of the inactivation of incretin hormones including glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). Dapagliflozin is an inhibitor of SGLT2 which reduces renal reabsorption of glucose leading to its increased urinary excretion. The two therapies therefore have complementary mechanisms of action in the treatment of T2DM.

Both saxagliptin and dapagliflozin are approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. Saxagliptin was registered in Australia in 2011 and is indicated as a combination therapy with metformin, a sulphonylurea, a thiazolidinedione or insulin. Dapagliflozin was registered in Australia in 2012 and is indicated in conjunction with metformin or other anti-hyperglycaemics. It is also indicated as monotherapy when treatment with metformin is not tolerated.

Diabetes treatment aims to achieve glucose and metabolic control. The sponsor proposes that early intensive diabetes treatment is beneficial but the risk of hypoglycaemia has been an important barrier. Therefore, effective glucose lowering therapies with a low risk of hypoglycaemia are necessary. The sponsor states in the Clinical Overview that the FDC offers a new treatment option to patients with inadequate glycaemic control with the potential to achieve an effective and sustained HbA1c reduction (saxagliptin and dapagliflozin), glucose dependent insulin secretion (saxagliptin), improvement in insulin sensitivity (dapagliflozin), modulation of glucagon response (saxagliptin), and body weight reduction and modest BP lowering (dapagliflozin). At the same time, the glucose sensor like effect of these two agents results in a low risk of hypoglycaemia.

The FDC offers a novel combination in the treatment of T2DM. In the rationale proposed by the sponsor, it is stated that the dual therapy of saxagliptin/dapagliflozin would be an add-on to metformin.

[2] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[3] Category B3: 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 foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Comment: This use as an add-on to metformin has not been reflected in the proposed indication.

Guidance

The saxagliptin/dapagliflozin FDC clinical development programme was designed in accordance with published guidelines.[4] The sponsor stated that both the saxagliptin and dapagliflozin clinical development programmes were designed in accordance with EU[5] and US[6] guidelines. Cardiovascular outcome studies include the completed SAVOR study for saxagliptin and the Dapagliflozin Effect on Cardiovascular Events (DECLARE) study which is ongoing and expected to be completed by second-third quarter 2019.

Contents of the clinical dossier

The submission contained the following clinical information:

- Two clinical pharmacology studies undertaken in healthy subjects, which contain pharmacokinetic data (CV181341, and CV181191) and two analytical method reports. There were no population pharmacokinetic analyses.
- Three Phase III efficacy/safety studies (CV181168, MB102129 and CV181169).
- Statistical analysis plan and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The sponsor stated in the Clinical Overview that the clinical development programme was conducted in accordance with ICH GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 2: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence† - Single dose	CV181341	BE of FDC tablet containing 5 mg saxagliptin/10 mg dapagliflozin relative to a free combination of 5 mg

[4] European Medicines Agency, "Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009.
[5] European Medicines Agency, "Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00)", 30 May 2002; European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)", 14 May 2012.
[6] Food and Drug Administration Center for Drug Evaluation and Research, "Guidance for Industry: Diabetes Mellitus - Developing Drugs and Therapeutic Biologics for Treatment and Prevention", February 2008.

PK topic	Subtopic	Study ID	*
			saxagliptin and 10 mg dapagliflozin tablets in the fasted and fed state
PK interactions	Active components of the FDC	CV181191	To assess DDIs between a single 5 mg oral dose of saxagliptin and 10 mg oral dose of dapagliflozin

* Indicates the primary aim of the study; † Bioequivalence of different formulations; DDI - drug-drug interaction

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

Evaluator's conclusions on pharmacokinetics

- Qtern is to be administered orally, once daily with or without food.

ADME

- Under both fasted and fed conditions saxagliptin was rapidly absorbed with median Tmax values (range) of 0.60 h (0.25-1.50) and 1.00 h (0.50-4.00) under fasted and fed conditions, respectively. For dapagliflozin, the Tmax values (range) were 1.00 h (0.50-3.00) and 2.50 h (0.50-8.08) for fasted and fed subjects, respectively.
- Following oral administration of a single dose in healthy subjects, Qtern was bioequivalent with a free combination of 5 mg saxagliptin and 10 mg dapagliflozin tablets.
- The small differences in dapagliflozin and saxagliptin exposure seen following a single oral dose administration of Qtern in the fed and fasted states are unlikely to be clinically significant.
- Following a single dose of Qtern to fasted healthy subjects the Cmax, AUCinf, Tmax and t1/2 values for 5-OH saxagliptin were 53.9 ng/mL, 323 ng.h/mL, 1.50 h and 16.3 h, respectively.

Inter-subject variability

- The inter-subject variability in the Cmax and AUCinf values for dapagliflozin following a single oral dose of Qtern in the fasted state were 40% and 21%, respectively, for saxagliptin were 32% and 23%, respectively, and for 5-OH saxagliptin were 28% and 18%, respectively.

DDIs

- Following a single oral dose of the free combination of 5 mg saxagliptin and 10 mg dapagliflozin the PK parameters of each of the active components were similar to when 5 mg saxagliptin or 10 mg dapagliflozin were administered alone.

Limitations of the PK studies

- No studies examined the PK of Qtern in the target population or in other special populations.
- No studies examined the drug-drug interaction between Qtern and other drugs.

Questions related to the PK studies

- Can the sponsor please confirm that the Onglyza and Forxiga tablets used in Studies CV181341 and CV181191 are identical to the formulations registered in Australia?
- Can the sponsor please confirm that the Qtern formulation used in Study CV181341 is identical to the formulation that is to be marketed in Australia?

Pharmacodynamics

No dedicated PD studies were undertaken as part of this submission.

Dosage selection for the pivotal studies

The dosage selected for the FDC is the approved dosages for saxagliptin (5 mg) and dapagliflozin (10 mg).

> *Comment: The recommended dose for saxagliptin is 5 mg once daily. However, in patients with moderate to severe renal impairment (CrCl ≤50 mL/min), the recommended dose is 2.5 mg per day (saxagliptin is not recommended for use in patients with severe renal impairment or end-stage disease). A FDC including 2.5 mg saxagliptin has not been proposed.*

Efficacy

Studies providing efficacy data

- Pivotal efficacy studies: Study CV181169, Study CV181168, Study MB102129

> *Comment: The three included clinical trials were sponsored by Bristol-Myers Squibb.*

Evaluator's conclusions on efficacy

The dossier included three Phase III clinical efficacy studies (CV181169, CV181168 and MB102129) in adults with T2DM. They were all randomised, double blind, placebo controlled studies with an open label lead in period followed by a 24 week double blind treatment period. Studies CV181168 and MB102129 also have ongoing 28 week blinded extension treatment periods which have not been reported in this dossier.

In all studies, saxagliptin dose was 5 mg daily and dapagliflozin dose was 10 mg daily. The three efficacy studies assessed free combination of therapies rather than the FDC formulation. In Studies CV181168 and MB102129, metformin immediate release (IR) was used, while in CV181169 metformin XR was used. Subjects were on a stable dose of background metformin and the dose in all studies was ≥1500 mg per day.

Study CV181169 compared triple therapy of dapagliflozin 10 mg, saxagliptin5 mg and metformin to dual therapy dapagliflozin + metformin, or saxagliptin + metformin, in those inadequately controlled on metformin monotherapy. CV181168 and MB102129 assessed triple therapy in those inadequately controlled on dual therapy. CV181168 assessed the addition of saxagliptin to dapagliflozin plus metformin compared to dapagliflozin plus metformin dual therapy. MB102129 assessed the addition of dapagliflozin to saxagliptin plus metformin compared to saxagliptin and metformin dual therapy. To aid recruitment this latter study had two strata for screening and open label therapy: those on metformin monotherapy and those on metformin plus a DPP4 inhibitor.

The primary efficacy endpoint for all studies was the adjusted mean change from baseline to Week 24 in HbA1c. Secondary endpoints included 2 hour PPG (from MMT), FPG, body

weight and proportion achieving HbA1c <7.0%. Statistical analyses were similar across the studies and multiplicity was controlled using a hierarchical testing procedure. Analysis was conducted on all randomised subjects who took at least one dose of double-blind study medication.

For enrolment subjects were not adequately controlled on metformin monotherapy with an HbA1c ≥8.0% to ≤12.0% in study CV181169, and ≥8.0% to ≤11.5% in studies CV181168 and MB102129 except for stratum B (prior dual therapy) where it was ≥7.5% to ≤10.5%. In these latter two studies subjects needed an HbA1c of 7.0% to ≤10.5% on dual therapy for randomisation.

The studies appeared well conducted with low rates of major protocol deviations, high treatment compliance and high completion rates. The number randomised was 534, 315 and 320 in CV181169, CV181168 and MB102129, respectively and study completion rates were 92-95%. The treatment groups were relatively well balanced in terms of baseline demographics and disease characteristics. Subjects were generally White, with a mean age of 54-55 years, mean BMI of approximately 31-32 kg/m^2, and the mean diabetes duration was approximately 7 to 8 years. After open label therapy, the mean baseline HbA1c was 8.9% in CV181169, 7.9% in CV181168 and 8.2% in MB102129.

All three studies met their primary endpoint demonstrating a greater reduction in HbA1c after 24 weeks treatment with saxagliptin + dapagliflozin + metformin compared to saxagliptin + metformin (studies CV181169 and MB102129) or dapagliflozin + metformin (studies CV181169 and CV181168). The adjusted mean treatment difference in HbA1c for Saxa + Dapa + Met compared to Dapa + Met was -0.35% in CV181168 and -0.27% in CV181169. The difference for Saxa + Dapa + Met compared to Saxa + Met was -0.59% in CV181169 and -0.72% in MB102129. The addition of dapagliflozin to saxagliptin plus metformin had a greater incremental effect on HbA1c than adding saxagliptin to dapagliflozin plus metformin.

In general, the treatment effect on HbA1c was generally greater in those with higher baseline HbA1c (>9.0%). Subgroup analysis of non-White racial groups was not possible due to small numbers. There was a possible interaction found in two of the studies with women ≤50 years having smaller reduction in HbA1c. The small group size makes assessing this effect difficult; however, the sponsor has been asked to comment on this finding.

In Studies CV181169 and CV181168, no statistically significant difference in the secondary endpoint of PPG was found so hierarchical testing ceased at this point. In MB102129, Saxa + Dapa + Met had a significantly greater effect on PPG than saxagliptin + metformin (difference of -1.97 mmol/L). It was noted that in CV181169 there was a numerically greater reduction in PPG with Saxa + Dapa + Met compared to Saxa + Met of -2.44 mmol/L while this was not evident compared to Dapa + Met (-0.51 mmol/L).

Changes in FPG were similar between Saxa + Dapa + Met and dapagliflozin + metformin and greater than with saxagliptin + metformin. After 24 weeks treatment, the percentage of subjects achieving an HbA1c <7.0% was greater with Saxa + Dapa + Met than dual therapy: 41.4% vs 18.3% (Saxa + Met) and 22.2% (Dapa + Met) in CV181169; 35.3% versus 23.1% (Dapa + Met) in CV181168; and 38.0% versus 12.4% (Saxa + Met) in MB102129.

Analysis of mean change from baseline to Week 24 in body weight found reductions in groups treated with dapagliflozin from 0.51 to 2.39 kg. Weight reduction in CV181168 was less presumably as subjects had already received open label dapagliflozin.

Discontinuation due to lack of glycaemic control or use of rescue medication was highest with saxagliptin plus metformin: 9.4% (CV181169) and 15.4% (MB102129) compared to 3.4%-4.4% with dapagliflozin plus metformin and 1.8%-5.5% with triple therapy.

Efficacy of saxagliptin/dapagliflozin with metformin after 1 year of treatment (studies CV181168 and MB102129) has not been provided. It was stated in the Clinical Overview that the studies will be completed in Q3 2015.

The efficacy studies were designed in accordance with the EMA guidelines on the development of a FDC.[7] Patients insufficiently controlled on metformin or dual therapy (one constituent of the FDC + metformin) were assessed in parallel groups with placebo controls. The design of the studies was also in accordance with EMA guidelines on products for treatment of diabetes.[8] This included use of HbA1c for the primary endpoint, appropriate statistical methods, analysis of HbA1c responders, a representative population, balanced treatment groups, and demonstration of superiority over placebo. While the studies provided confirmatory data to 24 weeks, the requirement of having, at least, one confirmatory study demonstrating maintenance of effect over at least 12 months has not been met.

Safety

Studies providing safety data

Safety data were provided from the three Phase III studies (CV181169, CV181168, MB102129) with some supportive data from two Phase I healthy volunteer studies (CV181341 and CV181191). Safety data collected were: general AEs, AEs of particular interest; clinical laboratory tests, vital signs, 12 lead ECGs and physical examination. Hypoglycaemia was collected on a specific case report form (CRF) page and classified as major, minor and other.[9] Only hypoglycaemia episodes that were SAEs were analysed with the AE data.

Data were pooled from the three phase III studies up to the week 24 efficacy assessment (short term [ST] treatment). This was termed the Integrated ST Pool. Data were based on all treated subjects.

There was a Clinical Event Committee (CEC) which adjudicated suspected cardiovascular events and an independent Hepatic Adjudication Committee which reviewed blinded data on liver-related abnormalities (hepatic disorders and laboratory abnormalities) to determine whether they were drug induced.

Patient exposure

The integrated ST Pool included 1169 subjects: 492, 336 and 341 who received Saxa + Dapa + Met, Saxa + Met and Dapa + Met, respectively. The median treatment duration for both saxagliptin and dapagliflozin was 169 days across the three treatment groups with a range of 1 to 223 days. There were few (n = 9) subjects aged 75 years or older in the development program with only 4 receiving Saxa + Dapa + Met therapy.

[7] European Medicines Agency, "Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009.
[8] European Medicines Agency, "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)", 14 May 2012.
[9] Hypoglycaemia major episode was defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a glucose value <3 mmol/L (<54 mg/dL) and prompt recovery after glucose or glucagon administration. Minor episode was defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL), regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL) that does not qualify as a major episode. Other episode of hypoglycaemia was defined as suggestive episode reported but not meeting the criteria for major or minor episodes.

Comment: All exposure in the clinical efficacy and safety studies was to the free combination of saxagliptin and dapagliflozin.

There were 72 and 42 healthy volunteers in Studies CV181341 and CV181191, respectively, who were dosed with study treatment. Of these, 72 subjects in CV181341 received the FDC with 36 receiving the 2.5/5 mg dose and 36 receiving the 5/10 mg dose. Subjects in CV181191 received free combination saxagliptin and dapagliflozin.

Safety issues with the potential for major regulatory impact

The major safety issues with the FDC are the same as those identified for the individual components.

In the saxagliptin RMP the important identified risks are hypersensitivity reactions, pancreatitis, infections and GI related AEs. The important potential risks are skin lesions (ulcers, erosions, and necrosis), lymphopaenia, hypoglycaemia , severe cutaneous adverse reactions, opportunistic infections, pancreatic cancer and cardiac failure.

In the dapagliflozin RMP, the important identified risks are genital infections and UTIs. The important potential risks are hypoglycaemia, volume depletion and the clinical consequences of increased haematocrit, renal impairment/failure, hypersensitivity reactions, bone fracture, liver injury, bladder cancer, breast cancer, prostate cancer and off-label use of dapagliflozin in specific populations.

Post marketing data

No post-marketing data were included in the dossier.

Evaluator's conclusions on safety

The three Phase III studies in the dossier assessed a free combination of saxagliptin plus dapagliflozin in conjunction with metformin and compared this triple therapy to dual therapy of saxagliptin plus metformin or dapagliflozin plus metformin. Consequently, the safety of saxagliptin/dapagliflozin combination was only available with concomitant metformin and only in comparison to either dual therapy (Saxa + Met or Dapa + Met). In addition, the safety of the FDC must be extrapolated from that found with the free combination.

Safety data were pooled from the three Phase III studies up to the week 24 efficacy assessment (termed the Integrated Short Term Pool). There was a Clinical Event Committee which adjudicated suspected cardiovascular events and an independent Hepatic Adjudication Committee which reviewed blinded data on liver-related abnormalities.

The integrated ST Pool included 1169 subjects: 492, 336 and 341 who received Saxa + Dapa + Met, Saxa + Met and Dapa + Met, respectively. The median treatment duration for both saxagliptin and dapagliflozin was 169 days across the three treatment groups. There were also 113 healthy volunteers who received saxagliptin plus dapagliflozin in Phase I studies of whom 72 received the FDC, though only 36 received the proposed 5/10 mg strength.

Overall, the safety of the saxagliptin plus dapagliflozin in combination with metformin was in line with the dual therapy combinations. There were no deaths during the 24 weeks of double blind treatment and the SAE rate was similar between groups (2.4%, 2.7% and 2.1%). There were two treatment related SAEs: hyperkalaemia in a subject who received saxagliptin plus metformin and thrombocytopaenia in a subject on saxagliptin plus dapagliflozin and metformin which was considered possibly drug induced.

Treatment discontinuation was slightly higher with the Saxa + Dapa + Met therapy (2.0% vs 0.6%, 1.2%) and the discontinuation events that occurred in more than one patient were decreased GFR and pollakiuria (2 cases each).

The AE rates were similar between groups with the most frequent AEs in the Saxa + Dapa + Met group being nasopharyngitis, headache, UTI, influenza and back pain. Rates of AEs were also similar when examining concomitant addition of saxagliptin and dapagliflozin (Study CV181169) compared to sequential addition (CV181168 and MB102129). Total treatment related AE rates were no higher with Saxa + Dapa + Met, although renal and urinary disorders were higher (2.4% vs 0.6% and 1.5%) (the most frequent pollakiuria: 1.2% versus 0.3% and 0.6%).

The rate of hypoglycaemia was similar with triple therapy and dapagliflozin + metformin (1.2% versus 1.8%), however it was higher than with saxagliptin + metformin (1.2% versus 0.3%). No cases were classed as major (symptomatic requiring external assistance and glucose <3 mmol/L).

Renal impairment or failure occurred at a similar rate in subjects receiving saxagliptin plus metformin and higher than those receiving dapagliflozin plus metformin (1.4%, 1.8% and 0.6%). Compared to dual therapy there was no increased risk of infections including genital or urinary infections.

Adjudicated cardiovascular events also occurred at a similar frequency (0.8%, 0.6% and 0.6%). AEs related to cardiac failure were slightly more frequent in the saxagliptin containing treatment groups (1.0%, 0.9% versus 0.6%). The sponsor reported that the Phase IV cardiovascular outcome study of saxagliptin (SAVOR) found an increased risk compared to placebo of hospitalisation due to cardiac failure (HR 1.27, 95% CI: 1.07, 1.51).

Independent adjudication of hepatic events found similar rates (0.8%, 0.9% and 0.6%). Three cases were deemed possibly treatment related (all in dual therapy groups), were classed a grade I hepatocellular injury, and there were no cases of DILI.

Although there was no relevant mean change in creatine kinase, there was a higher rate of CK >5xULN (1.2% vs 0%) in those treated with saxagliptin plus dapagliflozin and metformin. Similarly, there was a slightly higher rate of potassium (≥6.0 mEq/L) with triple therapy (2.3% versus 0.9%, 1.2%). The sponsor stated these cases were not persistent and were not reflected in treatment discontinuation. The triple therapy and dapagliflozin plus metformin groups showed minor increases in haematocrit and haemoglobin; however, the rate of markedly abnormal levels was in line with dual therapy groups. While there were similar rates of microscopic haematuria, there was a slightly higher rate of haematuria AEs with Saxa + Dapa + Met (0.6% versus 0% and 0.3%). Other laboratory assessments were unremarkable.

Subjects treated with dapagliflozin containing regimens were found to have small decreases in mean SBP and DBP (up to -1.7 mmHg) which is consistent with its diuretic effect.

The limitations of the safety data included: a lack of data in subjects aged 75 years or older; insufficient Asian patients to examine safety in this subgroup; no data on pregnancy or lactation; and safety data was only available for up to 24 weeks of treatment.

The safety database was relatively small in size (n = 492) making determination of risks difficult. Nonetheless, the level of knowledge on the constituents is larger and can be directly applied to this product.

There was no indication of a pharmacokinetic interaction between saxagliptin and dapagliflozin. In addition, there was no proposed change in the dosing in the FDC from that approved for the individual components.

The lack of the saxagliptin 2.5 mg dose, together with known dapagliflozin risks, mean that the treatment is unsuitable for patients with a CrCl <60 mL/min.

Overall, within the limitations of a relatively small safety dataset size, the addition of saxagliptin and dapagliflozin to metformin did not appear to result in an increase in safety risks, and in particular the risk of hypoglycaemia, compared to treatment with saxagliptin and metformin or dapagliflozin and metformin after 24 weeks of treatment. The safety data to 52 weeks should to be provided to further elucidate risks with longer term treatment.

It has been noted in the US label for saxagliptin has an included risk of severe disabling arthralgia with DPP4 inhibitors. This has not been included in the proposed PI and a question has been raised.

First round benefit-risk assessment

First round assessment of benefits

The benefits of saxagliptin/dapagliflozin in the proposed usage are:

- When given together with metformin there is a consistent reduction in HbA1c that is greater than with saxagliptin plus metformin or dapagliflozin plus metformin.
- When given together with metformin, a higher proportion of patients achieved glycaemic control of HbA1c <7.0% after 24 weeks treatment than with saxagliptin plus metformin or dapagliflozin plus metformin.
- A complementary mechanism of action of the two therapies.
- No major hypoglycaemia events reported in the development program.
- No new safety signals.

First round assessment of risks

The risks of saxagliptin/dapagliflozin in the proposed usage are:

- Hypoglycaemia, with a greater risk for saxagliptin + dapagliflozin + metformin than with saxagliptin + metformin but in line with dapagliflozin + metformin.
- Other risks as identified for the individual components such as volume depletion, hypotension, electrolyte imbalances, hypersensitivity reactions, UTIs, genital infections, skin disorders, pancreatitis, cardiac failure and increased haematocrit.
- The combination cannot be used in patients with moderate to severe renal impairment, in patients with severe hepatic impairment or during pregnancy or lactation.
- The combination must be used with caution in patients with cardiac failure.
- A lack of data in patients 75 years and older and a greater risk in the elderly of volume depletion.
- A lack of efficacy and safety data beyond 24 weeks.

First round assessment of benefit-risk balance

The FDC of saxagliptin and dapagliflozin combines two anti-hyperglycaemic products with differing modes of action and this complementary action has the potential to be of use to clinicians. Combining two treatments in one tablet also has a possible benefit to patients of

increased treatment compliance via convenience, although no data have been presented on this.

The three clinical efficacy and safety studies were conducted with a free combination of saxagliptin and dapagliflozin so it was crucial that the bioequivalence of the free to FDCs was demonstrated. In addition, there was no evidence of drug-drug interactions between the FDC components.

The combination of saxagliptin and dapagliflozin plus metformin resulted in a consistent and statistically significant greater reduction in HbA1c, and a greater proportion of subjects achieving an HbA1c response of <7.0%, than with dual therapy of saxagliptin or dapagliflozin plus metformin. The level of additional benefit, in terms of HbA1c reduction, of the third therapy over dual therapy (saxagliptin + metformin or dapagliflozin + metformin) was however only modest (-0.27% to -0.35% when adding saxagliptin and -0.59% to -0.72% when adding dapagliflozin). The effect on secondary endpoints of FPG and PPG was of variable significance, particularly when saxagliptin + dapagliflozin +metformin therapy was compared to dapagliflozin + metformin. Consistent with known effects, dapagliflozin groups demonstrated the benefit of small levels of weight reduction.

Within the confines of a moderate sized safety dataset, no new safety signals were identified for the combination of saxagliptin plus dapagliflozin and metformin. In particular, the risk of hypoglycaemia was no greater than with dapagliflozin plus metformin. There was also no increased risk of cardiac failure from the analysis of adjudicated CV events. There were no efficacy or safety data beyond 24 weeks treatment and so the data to 52 weeks from the two Studies CV181168 and MB102129 should be submitted to further characterise the longer term safety and efficacy.

The proposed indication is that the FDC should be used *as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.*

The evaluator believes that this indication is too broad. Firstly, the clinical trials only assessed efficacy and safety of saxagliptin and dapagliflozin when given in combination with metformin. Therefore, the indication must include metformin to accurately reflect the available clinical data.

Secondly, the sponsor proposes that the FDC could be the next step after metformin, that is, as a concomitant dual add-on second line therapy. The sponsor puts forward an argument that there may be

> *delays in intensifying treatment* which *may contribute to poor level of glycaemic control in patients with T2DM*.

Therefore, there is a clinical need for a concomitant add-on approach to enable patients to reach glycaemic goals earlier and the proposed FDC would facilitate this.

While it is acknowledged that initial combination therapy may allow patients to achieve HbA1c targets more quickly, the evaluator notes that in the ADA/EASD position statement on management of hyperglycaemia in T2DM,[10] it was stated that:

> *there is no proven overall advantage to achieving a glycemic target more quickly by a matter of weeks or even months. The article goes on to state that as long as close patient follow-up can be ensured, prompt sequential therapy is a reasonable alternative, even in those with baseline HbA1c levels in this range [≥9%].*

The recommendations in the article are that if the HbA1c target is not achieved after 3 months of dual therapy then treatment should proceed to a three drug combination.

[10] Inzucchi SE, et al. Management of hyperglycaemia in type 2 diabetes, 2015: A patient-centered approach. *Diabetes Care* 38: 140-149 (2015).

Taking these recommendations into account, the relatively modest reduction in HbA1c, the risks of the two therapies, the lack of long term outcome data with dapagliflozin, and the general recommendations on the rational use of prescription therapies, the evaluator believes that use of the saxagliptin/dapagliflozin combination should as third line therapy in conjunction with metformin. As such, the indication should be reworded to reflect this.

The FDC has not been approved in the US and the sponsor has been requested to provide the reasons for this.

In summary, the evaluator finds that the benefit-risk balance of saxagliptin/dapagliflozin FDC is unfavourable given the proposed usage. Should the issues outlined be addressed to the TGA's satisfaction, then the benefit-risk balance may become favourable.

First round recommendation regarding authorisation

It is currently not recommended to authorise the FDC of saxagliptin/ dapagliflozin 5/10 mg due to the following issues:

- The indication needs to be reworded to reflect the requirement for treatment to be in conjunction with metformin. It is also recommended that the FDC be used as a third line therapy.
- There are a number of recommendations for changes to the draft PI and CMI which should be addressed.
- In addition, if available now, the longer term efficacy and safety data to 52 weeks of treatment should be provided for evaluation. Otherwise, it should be submitted as soon as available.

Clinical questions

Pharmacokinetics

- Question 1: Can the sponsor please confirm that the Onglyza and Forxiga tablets used in Studies CV181341 and CV181191 are identical to the formulations registered in Australia?
- Question 2: Can the sponsor please confirm that the Qtern formulation used in Study CV181341 is identical to the formulation that is to be marketed in Australia?

Pharmacodynamics

Not applicable.

Efficacy

- Question 3: In the efficacy studies a possible interaction was found in women ≤50 years who had a smaller reduction in HbA1c. It is acknowledged that the small group size makes assessing this effect difficult, however could the sponsor please comment on this finding?

Safety

- Question 4: In the US label for saxagliptin, there is a warning for severe disabling arthralgia with DPP4 inhibitors. This risk has not been included in the proposed label

for the saxagliptin/dapagliflozin FDC. Please discuss these findings and include relevant data in the proposed PI.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU RMP (version 1, dated 1 April 2015, DLP 25 September 2014) with an ASA (version 1, dated 7 August 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Ongoing safety concerns.

Important identified risks	Hypersensitivity reactions Infections Genital infections Urinary tract infections Pancreatitis Gastrointestinal-related AEs
Important potential risks	Hypoglycaemia Lymphopaneia Severe cutaneous adverse reactions Pancreatic cancer Skin lesions (ulcer, erosion, necrosis) Opportunistic infections Cardiac failure Volume depletion Clinical consequences of increased haematocrit Renal impairment/failure Bone fracture Liver injury Bladder cancer Breast cancer Prostate cancer Off-label use of saxagliptin/dapagliflozin FDC in specific populations
Missing information	Paediatric population Elderly population

Important identified risks	Hypersensitivity reactions Infections Genital infections Urinary tract infections Pancreatitis Gastrointestinal-related AEs
	Pregnancy and lactation/breastfeeding Moderate and severe hepatic impairment Severe renal impairment Patients with immunocompromised conditions Use in patients with malignancy/neoplasm

In addition, the following missing information items, adopted as Australian-specific safety concerns for the single ingredient dapagliflozin product, also apply to this FDC and are included in the ASA:

- Malignancy
- Off-label use in obese patients who do not have T2DM
- Urosepsis
- Patients with BMI > 45

RMP reviewer comment

Subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, it is recommended that:

- Diabetic ketoacidosis (DKA) should be added as an important potential risk. In response to a previous application for dapagliflozin, the sponsor committed to including DKA as an important potential risk. This safety concern was described in the US FDA and TGA advisories regarding cases of DKA associated with SGLT2 inhibitors.
- It is noted that 'Congestive heart failure NYHA class III and IV' which appears as an item of missing information specific to dapagliflozin is not included in the summary of the safety concerns for the FDC. This omission should be clarified by the sponsor.

Otherwise, subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, the summary of safety concerns consolidates the previously accepted risks for dapagliflozin and saxagliptin.

Pharmacovigilance plan

Routine pharmacovigilance[11] is proposed for all safety concerns.

According to the sponsor, there are also some additional pharmacovigilance activities specific to the single ingredient products, which are also ongoing or planned for the saxagliptin/dapagliflozin FDC.

[11] Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

RMP reviewer comment

A number of activities included in the prospective pharmacovigilance plan have milestones which have already passed. The sponsor should confirm which activities remain ongoing and which have been completed. The RMP documentation should be updated to reflect the status of these activities.

The sponsor is advised that the "safety concerns addressed" column of the EU-RMP should include the actual safety concern as it appears in the summary of safety concerns. This should be addressed when the EU-RMP is next updated for clarity and consistency.

The sponsor should confirm whether patients prescribed the saxagliptin/dapagliflozin FDC will be included in Study MB102209 or indeed any pharmacovigilance activity.

The sponsor should confirm whether any additional post-marketing activities, specific to the FDC have or are anticipated to be required as a result of concurrent evaluations by the EMA and FDA.

It is noted that the activities described in the pharmacovigilance plan are generally consistent with that proposed in the previously accepted RMPs for the single ingredient dapagliflozin and saxagliptin products. However, targeted questionnaires are employed for several important identified and potential risks for the single ingredient saxagliptin and dapagliflozin products and the sponsor should clarify whether the same applies to the FDC.

Protocols of ongoing studies are not assessed as part of the RMP evaluation. It is expected that results of these activities will be communicated to the TGA in appropriate manner, such as an application to change the product registration details, routine reporting (for example, PSUR) or other mechanisms in accordance with pharmacovigilance obligations.

Risk minimisation activities

Routine risk minimisation activities[12] are proposed to mitigate the risks associated with the saxagliptin/dapagliflozin FDC.

No additional risk minimisation activities are specifically proposed for the FDC.

RMP reviewer comment

According to the ASA, "Speaker training slides" and a "Prescribers and Patient Brochure" are currently ongoing for dapagliflozin. Further details regarding the relevance of this activity to the FDC are sought.

In that absence of additional risks specific to the FDC, routine risk minimisation may be acceptable.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

"Safety considerations may be raised by the clinical evaluator…"

[12] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

Sponsor response

The nonclinical and clinical evaluation reports do not include comments warranting revision of the RMP.

Evaluator's comment

This response is acceptable. It is noted that a safety consideration 'severe disabling arthralgia' was identified by the clinical evaluator as a risk associated with saxagliptin and that the sponsor has updated the proposed PI as a risk minimisation measure. No further action is recommended.

Recommendation #2 in RMP evaluation report

The PI Dosage and Administration section states: The safety and efficacy of this medicine in combination with GLP-1 analogues, insulin and its analogues, or sulfonylurea has not been established. However the single ingredient saxagliptin and dapagliflozin products are permitted for use in combination with insulin and sulfonylureas. Given this current situation, it may not be self-evident to a prescriber that safety and efficacy of the FDC combined with an insulin or sulfonylurea has not been established. From a risk minimisation perspective it is therefore recommended that more appropriate emphasis is included in the indication statement regarding permitted combinations.

Sponsor response

The proposed PI currently includes statements in two separate locations (that is, Precautions and Dosage and Administration) indicating that safety and efficacy of the FDC has not been established with GLP-1 analogues, insulin and its analogues, or insulin secretagogues such as sulfonylureas. The sponsor considers the existing text and location of the statements sufficient to ensure the safe and appropriate use of the FDC and a further amendment to the proposed indication is not required.

Evaluator's comment

The sponsor's response is noted. This is acceptable in the context of the RMP evaluation, pending the delegate's consideration.

Recommendation #3 in RMP evaluation report

DKA should be added as an important potential risk. In response to a previous application for dapagliflozin, the sponsor committed to including DKA as an important potential risk. This safety concern was described in the US FDA and TGA advisories regarding cases of DKA associated with SGLT2 inhibitors.

Sponsor response

In alignment with the next version of the EU-RMP for dapagliflozin-containing products, the sponsor will include diabetic ketoacidosis (with atypical presentation) as an important identified risk based on the request from the EMA.

Evaluator's comment

The sponsor has not yet submitted an ASA or EU-RMP with updated safety concerns including 'Diabetic Ketoacidosis'. It is recommended that the important potential risk 'Diabetic Ketoacidosis' be included in the safety concerns and satisfactory pharmacovigilance and risk minimisation plans addressing it be developed.

Recommendation #4 in RMP evaluation report

'Congestive heart failure NYHA class III and IV' which appears as an item of missing information specific to dapagliflozin is not included in the summary of the safety concerns for the FDC. This omission should be clarified by the sponsor.

Sponsor response

The sponsor will include Congestive heart failure NYHA class III and IV as an item of missing information in the summary of safety concerns for Qtern in accordance with the revised EU-RMP.

Evaluator's comment

The sponsor has not yet submitted an ASA or EU-RMP with updated safety concerns including 'Congestive heart failure NYHA class III and IV' as missing information. It is recommended that this missing information be added to the safety concerns and satisfactory pharmacovigilance and risk minimisation plans addressing it be developed.

Recommendation #5 in RMP evaluation report

A number of activities included in the prospective pharmacovigilance plan have milestones which have already passed. The sponsor should confirm which activities remain ongoing and which have been completed. The RMP documentation should be updated to reflect the status of these activities.

Sponsor response

The sponsor provided an updated summary table of all ongoing pharmacovigilance activities appended to the Section 31 response and a commitment to include the next updated ASA.

Evaluator's comment

The summary table of ongoing pharmacovigilance activities should include milestones for all ongoing studies (estimated dates of study reports) and indicate whether Australian patients are included for each study. It is noted that some of this information is presented in the EU-RMP. It is recommended that the "Summary of Ongoing and Completed Studies…" table be updated with the requested details and is included in the revised ASA.

Recommendation #6 in RMP evaluation report

The sponsor is advised that the "safety concerns addressed" column of the EU-RMP should include the actual safety concern as it appears in the summary of safety concerns. This should be addressed when the EU-RMP is next updated for clarity and consistency.

Sponsor response

In the creation of the Qtern EU-RMP, the sponsor has attempted to keep alignment with the monocomponent EU-RMPs, while still harmonising the presentation of the information.

Evaluator's comment

The table "Ongoing and planned additional pharmacovigilance studies/activities" should facilitate cross-referencing of studies and safety concerns and so the recommendation to use verbatim wording of the 'safety concerns addressed' is repeated. However, the sponsor's response is acceptable as the table is concise and legible.

Recommendation #7 in RMP evaluation report

The sponsor should confirm whether patients prescribed the saxagliptin/dapagliflozin FDC will be included in Study MB102209 or indeed any pharmacovigilance activity.

Sponsor response

There are no ongoing or planned additional pharmacovigilance studies or activities for saxagliptin/dapagliflozin FDC. In relation to the prescription monitoring study (Study MB102209), in October 2015 the decision was taken to close the study.

Evaluator's comment

The sponsor's response, taken in the context of the response below, is acceptable given that routine pharmacovigilance activities are mandated for the FDC and comprehensive additional pharmacovigilance activities are ongoing for the monocomponent products.

Recommendation #8 in RMP evaluation report

The sponsor should confirm whether any additional post-marketing activities, specific to the FDC have or are anticipated to be required as a result of concurrent evaluations by the EMA and FDA.

Sponsor response

No post-marketing activities have been proposed for the saxagliptin/dapagliflozin FDC, reviews in US and EU are still ongoing.

Evaluator's comment

This is considered acceptable; however, any new additional pharmacovigilance activities for the FDC product as a result of the EMA or FDA review processes should be included in updated RMPs.

Recommendation #9 in RMP evaluation report

It is noted that the activities described in the pharmacovigilance plan are generally consistent with that proposed in the previously accepted RMPs for the single ingredient dapagliflozin and saxagliptin products. However, targeted questionnaires are employed for several important identified and potential risks for the single ingredient saxagliptin and dapagliflozin products and the sponsor should clarify whether the same applies to the FDC.

Sponsor response

The sponsor plans to apply the same targeted questionnaires as are in place for the monocomponents as part of routine pharmacovigilance activities for the saxagliptin/dapagliflozin FDC. The proposed questionnaires are included in the RMP annex. As the targeted questionnaires are considered part of routine pharmacovigilance, they are not specifically listed within the body of the RMP.

Evaluator's comment

The sponsor's response is valid and acceptable. However, the RMP is a useful tool for consolidating all the proposed safety monitoring measures in a single document. The sponsor should consider listing the 'Targeted follow-up questionnaires' against the specific safety concerns addressed in the EU-RMP to fully document the pharmacovigilance system. This table should be presented within the ASA.

Recommendation #10 in RMP evaluation report

Protocols of ongoing studies are not assessed as part of the RMP evaluation. It is expected that results of these activities will be communicated to the TGA in appropriate manner, such as an application to change the product registration details, routine reporting (for example, PSUR) or other mechanisms in accordance with pharmacovigilance obligations.

Sponsor response

The sponsor will communicate the study results to TGA via routine reporting such as periodic benefit-risk evaluation reports (PBRERs), changes to product application or other appropriate methods in accordance with pharmacovigilance requirements.

Evaluator's comment

This is acceptable.

Recommendation #11 in RMP evaluation report

The sponsor should confirm that there are no specific additional risk minimisation activities proposed for the FDC and provide clarification that the "Speaker training slides" and "Prescribers and Patient Brochure for Dapaglifozin" do not specifically discuss the FDC product.

Sponsor response

The Sponsor confirms that there are no specific additional risk minimisation activities proposed for the FDC and that the "Speaker training slides" and "Prescribers and Patient Brochure for Dapagliflozin" do not specifically discuss the FDC product.

Evaluator's comment

This is acceptable.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

- The delegate has recommended changes to the safety concerns of the RMP:
  - DKA should be added as an identified potential risk,
  - Amputations (as a potential class related risk of SGLT-2 inhibitors) should be added as an important potential risk
  - CK elevation associated with musculoskeletal system adverse events should be added as an important potential risk.
- The 'Summary of Ongoing and Completed Studies' table (ongoing pharmacovigilance activities) is not satisfactory. It has been updated to show completed studies but is still missing certain required information (study milestones, inclusion of Australian patients).
- It is recommended to the sponsor that they list the 'Targeted follow-up questionnaires' against the specific safety concerns addressed in the EU-RMP to fully document the pharmacovigilance system.
- It is recommended that a revised RMP consisting of the latest EU-RMP and revised ASA with requested changes be submitted for evaluation.

Comments on the safety specification of the RMP

The following additions to the safety specification requested by the Delegate have not been reflected in the ASA:

Important potential risk: Diabetic Ketoacidosis (with atypical presentation)

The sponsor states that DKA has been added as an important potential risk to the safety concerns in the core RMP. It is recommended that the revised EU-RMP and ASA should be submitted with pharmacovigilance and risk minimisation activities addressing this risk.

Important potential risk: Amputations (as a class related risk of SGLT-2 inhibitors)

This is based on risk identified in association with canagliflozin use (another SGLT-2 inhibitor) and the resultant PRAC procedure reviewing the risk. The sponsor has stated that routine pharmacovigilance activities for amputation and related terms are ongoing and sufficient to detect any associated rise in amputations with dapagliflozin use, and that

no such signal has been identified. The sponsor has declined to add this risk to the safety concerns.[13]

It is recognised that prescribers are already aware of the risk of amputation in the diabetic population. However, the list of safety concerns should list all important identified and important potential risks. Any potential increased risk of amputation in this population is considered important, even if a direct causal link with dapagliflozin is only suspected and has not yet been proven. A structured pharmacovigilance system is required to adequately characterise this potential risk.

It is therefore recommended to the sponsor that amputations (as a possible class related risk of SGLT-2 inhibitors) be included on the list of important potential risks. Pharmacovigilance activities should be assigned to detect and characterise this important potential risk, and it should be addressed by risk minimisation measures.

Important potential risk: Raised CK associated with musculoskeletal system adverse events

The Delegate has identified CK elevations in the combination treatment (saxagliptin + dapagliflozin + metformin) group as a safety concern.

There is an increased incidence (1.2% versus 0%) of CK elevations >5xULN in subjects receiving combination treatment in the pooled long term + short term data set compared to saxagliptin + metformin. There was one case of marked CK elevation and rhabdomyolysis. The sponsor's review of these cases of CK elevation with Qtern was noted including the presence of confounding factors in many of the reported cases and no overlap between elevated CK and reported arthralgia or back pain.

It is recommended that 'CK elevation associated with musculoskeletal system adverse events in combination use of saxagliptin and dapagliflozin' should be included as an important potential risk in the safety specification. The public health consequence of this risk, if proven, would impact on the risk/benefit profile of the product. Therefore, assigning it as an 'important potential risk' and providing structured pharmacovigilance and risk minimisation activities to monitor and mitigate the risk is recommended. Should sufficient safety data from post market pharmacovigilance be obtained to disprove the potential association, the risk could then be removed from the safety concerns.

Important potential risk: Severe arthralgia

The Delegate requested that the important potential risk: severe arthralgia (a possible class related adverse effect of DPP4-inhibitors) be included in the safety concerns.

The sponsor states that, based on the clinical features observed, the risk of arthralgia does not impact the risk/benefit profile. The sponsor has addressed this risk by assigning routine risk minimisation content to address it in the form of entries to the PI under Precautions, Adverse effects and Post-marketing experience.

In terms of risk minimisation, the above approach is sufficient. Routine pharmacovigilance activity is sufficient to monitor this risk, and suspected cases of saxagliptin associated arthralgia should continue to be reported. Given the reported frequency, severity, reversibility without sequelae, and non-life threatening nature of this adverse event it is the RMP evaluator's opinion that the overall risk/benefit profile is not affected by this risk. From an RMP perspective, given the current knowledge of this risk, it is acceptable for the sponsor to consider that 'severe arthralgia' is not an 'important' potential risk and not to include it in the safety concerns. The sponsor is expected to update the safety concerns if there is any adverse change in the known safety profile of saxagliptin or DPP-4 inhibitor class drugs in regard to arthralgia.

[13] The sponsor addressed this in their pre-ACPM response, which is included in this AusPAR.

Key changes to the updated RMP

No revised EU-RMP or ASA were submitted.

An appendix to the Section 31 response contains a table: 'Summary of ongoing and completed studies for Dapagliflozin, Saxagliptin and Qtern' that the sponsor commits to including in future ASA updates.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *The EU-RMP version 1.0 (dated 1 April 2015, data lock point 25 September 2014), with ASA v1.0, (dated 22 April 2016), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).*

VI. Overall conclusion and risk/benefit assessment

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

Quality

This was considered to be acceptable.

Nonclinical

This was considered to be acceptable.

Clinical

Efficacy

The clinical studies all included the addition of saxagliptin and dapagliflozin to treatment with metformin. They used single dose not the FDC tablet.

- Study 181169: the use of combination therapy with dapagliflozin/metformin for patients with T2DM and poor glycaemic control currently treated on metformin XR, n = 534. The mean age was 53.8 years, 12.7% were > 65 years. The mean BMI was 31.7 kg/m^2, duration of diabetes 7.6 years, HbA1c 8.94%.
- Study 181168: the addition of saxagliptin to patients with inadequate glycaemic control with dapagliflozin and metformin, n = 315; mean baseline HbA1c 7.9%.
- Study 102129: the addition of dapagliflozin to patients with inadequate glycaemic control with saxagliptin and metformin.

The use of Qtern resulted in a statistically significant improvement in mean HbA1c compared to treatment with the individual products alone. The addition of dapagliflozin led to an improvement of HbA1c of 0.59% with significant changes in secondary endpoints fasting and post prandial blood glucose and percentage responders. The mean improvement in HbA1c with saxagliptin was less, 0.27%, which is just below the 3%

difference considered clinically meaningful. There was a trend to reduction in fasting and postprandial blood glucose which was in the right direction but not statistically significant. There was a significant improvement in % responders. Rescue medications were used in 6% of the triple therapy group, 10% of the saxagliptin/metformin group and 3% of the dapagliflozin/metformin group.

Table 4: Study CV181169: primary and secondary efficacy endpoints, 24-week double blind treatment period (randomised subjects).

EFFICACY ENDPOINT STATISTICS	SAXA+DAPA+MET N = 179	SAXA+MET N = 176	DAPA+MET N = 179
PRIMARY EFFICACY ENDPOINT			
HBA1C (%) AT WEEK 24			
N#	176	175	172
BASELINE MEAN (SD)	8.93 (1.186)	9.03 (1.053)	8.87 (1.174)
N##	158	143	151
ADJ. MEAN CHANGE FROM BSL. (SE)	-1.47 (0.0778)	-0.88 (0.0795)	-1.20 (0.0789)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	(-1.62, -1.31)	(-1.03, -0.72)	(-1.35, -1.04)
SAXA+DAPA+MET VS. SAXA+MET IN ADJ. MEAN CHANGE FROM BSL.			
DIFFERENCE (SE)	-0.59 (0.1112)		
95% CI FOR DIFFERENCE	(-0.81, -0.37)		
P-VALUE (*)	<0.0001 *		
SAXA+DAPA+MET VS. DAPA+MET IN ADJ. MEAN CHANGE FROM BSL.			
DIFFERENCE (SE)	-0.27 (0.1108)		
95% CI FOR DIFFERENCE	(-0.48, -0.05)		
P-VALUE (*)	0.0166 *		

Table 5: Study CV181169: HbA1c subgroup analysis by baseline HbA1c at 24 weeks.

Treatments	Adjusted Mean Change From Baseline by Baseline HbA1c		
	< 8.0%	≥ 8% <9.0%	≥ 9.0%
Saxa+Dapa+Met (n=179)	-0.80 (N=37)	-1.17 (N=56)	-2.03 (N=65)
Saxa+Met (n= 176)	-0.69 (N=29)	-0.51 (N=51)	-1.32 (N=63)
Dapa+Met (n=179)	-0.45 (N=37)	-0.84 (N=52)	-1.87 (N=62)
Treatment Comparisons	**Difference (95% CI)**		
Saxa+Dapa+Met *vs* Saxa+Met	-0.10 (-0.60, 0.39)	-0.66 (-1.03, -0.28)	-0.71 (-1.04, -0.38)
Saxa+Dapa+Met *vs* Dapa+Met	-0.35 (-0.81, 0.11)	-0.33 (-0.71, 0.05)	-0.16 (-0.50, 0.17)

Patients with a HbA1c >9% did better with the addition of dapagliflozin, patients with a lower HbA1c < 8% did better with the addition of saxaglitpin.

The addition of dapagliflozin to saxagliptin and metformin resulted in a mean improvement in HbA1c of 0.72% after 24 weeks. The addition of saxagliptin to patients on dapagliflozin and metformin resulted in an improvement in HbA1c of 0.35%. The data on long term treatment for 28 weeks showed a sustained effect. In these studies, the baseline HbA1c was around 1% lower at baseline than in the study previously described.

Table 6: Summary of glycaemic efficacy at Weeks 24 and 52 in Studies CV181168 and MB102129 excluding data after rescue.

	Study CV181168		Study MB102129	
	Saxa+Dapa+Met	Pla+Dapa+Met	Saxa+Dapa+Met	Pla+Saxa+Met
Proportion of subjects achieving glycaemic target of HbA1c <7%				
Week 24				
X/N#	51/150	39/160	58/158	21/158
% adj mean change from BL (95% CI)	35.3 (28.2, 42.4)	23.1 (16.9, 29.3)	36.7 (30.9, 45.1)	13.3 (7.0, 17.9)
	Diff vs pla+dapa+met (95% CI) 12.2 (3.4, 21.0)		Diff vs pla+saxa+met (95% CI) 25.5 (16.7, 34.4) p<0.0001	
Week 52				
X/N#	42/150	23/160	45/158	21/158
% adj mean change from BL at Week 52 (95% CI)	29.3 (22.5, 36.1)	13.1 (8.1, 18.2)	29.4 (22.7, 36.2)	12.6 (7.4, 17.9)
	Diff vs pla+dapa+met (95% CI) 16.2 (8.1, 24.2)		Diff vs pla+saxa+met (95% CI) 16.8 (8.4, 25.2)	
HbA1c change from baseline				
Week 24				
N	150	160	158	158
Adj mean change from BL (95% CI)	-0.51 (-0.63, -0.39)	-0.16 (-0.28, -0.04)	-0.82 (-0.96, -0.69)	-0.10 (-0.24, 0.04)
	Diff vs pla+dapa+met (95% CI) -0.35 (-0.52, -0.18) p<0.0001		Diff vs pla+saxa+met (95% CI) -0.72 (-0.91, -0.53) p<0.0001	
Week 52				
N	105	103	102	67
Adj mean change from BL (95% CI)	-0.38 (-0.53, -0.22)	0.05 (-0.11, 0.20)	-0.74 (-0.90, -0.57)	0.07 (-0.13, 0.27)
	Diff vs pla+dapa+met (95% CI) -0.42 (-0.64, -0.20)		Diff vs pla+saxa+met (95% CI) -0.81 (-1.06, -0.55)	

Adj Adjusted; BL Baseline; CI Confidence interval; Dapa Dapagliflozin; Pla Placebo; Saxa Saxagliptin.
N# is the number of randomized subjects with non-missing baseline and Week 24 LOCF values.
X is the number of responders.

Safety

The dossier contained only safety data for 24 weeks. A one-page summary of the long term safety was included in the Section 31 response. The total number of adverse effects seen in the clinical development program was similar for triple therapy compared to double therapy; however, there were more treatment discontinuations due to adverse effects in the triple therapy group.

Table 7: Overall AE summary: treated subjects.

	Treatment groups		
	Saxa + Dapa + Met N=492	Saxa + Met N=336	Dapa + Met N=341
At least 1 AE	250 (50.8)	187 (55.7)	157 (46.0)
At least 1 hypoglycaemia	6 (1.2)	3 (0.9)	6 (1.8)
At least 1 AE or hypoglycaemia	250 (50.8)	188 (56.0)	160 (46.9)
At least 1 related AE[a]	32 (6.5)	23 (6.8)	21 (6.2)
Deaths	0	0	0
At least 1 SAE	12 (2.4)	9 (2.7)	7 (2.1)
At least 1 related SAE[a]	1 (0.2)	1 (0.3)	0
SAE leading to discontinuation of study medication	3 (0.6)	2 (0.6)	0
AE leading to discontinuation of study medication	10 (2.0)	2 (0.6)	4 (1.2)
Hypoglycaemia leading to discontinuation of study medication	0	0	0

Table 8: SAEs.

	Saxa + Dapa+ met N=492	Sax + met N=336	Dapa + Met N=341
Total subjects	12 (2.4%)	9 (2.7%)	7 (2.1%)
Cardiac Disorders	3 (1 each MI, cardiac failure, VT)	0 + 1 chest pain	1 (AF) + 1 chest pain
Neoplasms	3	0	0
Respiratory	2 (1 with PE)	1 (PE)	1
Skin and subcutaneous tissue	2 (1 each diabetic foot and skin ulcer)	0	0
Blood and lymphatics	1 (thrombocytopenia)	0	0
GIT	1	2	1
Hepatobiliary	1	0	0
Vascular	1 (peripheral arterial thrombosis)	1 (DVT)	0
Infections and Infestations	0	2	0

	Saxa + Dapa+ met N=492	Sax + met N=336	Dapa + Met N=341
CNS	0	0	1(TIA)
Musculoskeletal	0	1 (arthritis)	0
Metabolic	0	1 (hyperkalaemia)	0
Reproductive	0	0	1 (benign prostatic hypertrophy.

Additional safety concerns:

- Those already in the PI;
- There have been safety concerns in relation to the risk of DKA for the SGLT2 inhibitors. These did not emerge in the clinical trials, and have been adequately described in the PI. The concerns around severe arthralgia with DDP-IV inhibitors have also been addressed in the PI;
- Safety alert from a clinical trial regarding the risk of amputations with canagliflozin.

AstraZeneca analysed the AE of 30 completed dapagliflozin studies of 12 or more weeks duration (including saxagliptin/dapagliflozin studies). Surgery, such amputations, is considered to be a procedure and hence is not generally recorded as adverse events. To identify potential amputation events a free text search of was conducted for the 30 completed studies. There were 19 non-traumatic lower limb amputations identified: 8 patients with 12 events in 9195 patients (8058.6 patient-years exposure) on dapagliflozin and 7 patients with 7 events in 4629 patients (4177.1 patient-years exposure) on control.

For the post-marketing findings on non-traumatic lower-limb amputations, AstraZeneca's global safety database was searched for all spontaneous adverse event reports up to 24 April 2016 in association with the use of dapagliflozin or the dapagliflozin/metformin FDC Free text search of the narratives for all dapagliflozin and dapagliflozin/metformin case reports in the database was performed. A total of 2 cases were identified.

The mechanism of action of amputations associated with canagliflozin was attributed to an effect of volume depletion, which is a class effect for SGLT-2 inhibitors. There is a problem with the accuracy of reporting of AE of amputations in the clinical trials, thus the data provided from the sponsor may not reflect the true risk. The Delegate would recommend amputations be included in the PI and RMP of all SGLT-2 inhibitors to better document this risk, and provide advice to clinicians to monitor feet (and thus avoid this AE).

- A safety alert has been issued by the FDA regarding the risk of acute renal injury with dapagliflozin and canagliflozin. The proposed PI for Qtern already includes labelling to cover this risk;
- FDA concerns regarding raised CK in the clinical trials

The sponsor has addressed the FDA's concerns about the raised CK in a request for more information made by the delegate before the ACPM.

Qtern musculoskeletal events

In the integrated Short-term plus Long-term (ST + LT) Pool, 119 of the 1169 enrolled subjects (10.2%) experienced 149 adverse events (AEs) in the Musculoskeletal and

Connective Tissue Disorders System Organ Class (SOC). This included 52 of 492 subjects (10.6%) in the saxagliptin + dapagliflozin + metformin group, 39 of 336 subjects (11.6%) in the saxagliptin + metformin group, and 28 of 341 subjects (8.2%) in the dapagliflozin + metformin group. The most common musculoskeletal AEs occurring in ≥2% of subjects were back pain, arthralgia, pain in extremity, and muscle spasm in any treatment group. The majority of musculoskeletal events were assessed as non-serious (98.6%), mild (60%) or moderate in intensity (37%), not treatment related (97.3%), and resolved (69%).69%). Only 2 of the 149 musculoskeletal AEs (1.3%) were serious, 4 (2.7%) AE were assessed as related to study drug by the Investigator, and 4 (2.7%) were deemed severe in intensity.

Arthralgia was reported in the saxagliptin development program. Back pain was described in the dapagliflozin development program.

Qtern CK

The sponsor has provided a review of the information of elevated CK across the three clinical trials (CV161169, CV181168 and MB 102129) during both short and long term studies. During that time, blood samples were taken every 2-12 weeks depending on the trial.

Among the 7 subjects with elevate CK > 5X ULN in the saxagliptin + dapagliflozin + metformin group:

- all were male;
- 4/7 were Black/African Americans;
- 4/7 were taking statins or fibrates;
- 5/7 had marked CK elevations;
- 6/7 had elevations during the short term study;
- 2/7 had elevations during randomisation;
- all subjects values returned to normal on retesting (it is unclear if the medications were stopped);
- in one subject with an elevation > 10X ULN, there was associated myalgia and raised AST. These AE were considered to be non-serious, moderate, and considered not related to the study treatment. The AE resolved without treatment interruption. there was a history of increased physical activity;
- No subject permanently discontinued the study drug.

There was one subject with rhabdomyolysis with CK elevation > 10X ULN. This event occurred in a subject who had been randomised to saxagliptin + dapagliflozin + metformin. This man developed syncope and rhabdomyolysis Day 280 and pyelonephritis Day 295. This subject had a history of T2DM, hypertension, obesity, benign prostatic hypertrophy, glaucoma and urinary retention. There was no information given as to whether there was associated muscle pain or myoglobinuria.

Only 2 patients in the saxagliptin + dapagliflozin + metformin group experienced musculoskeletal AE that were associated with elevated CK.

Saxagliptin musculoskeletal events

There was no imbalance with arthralgia, back pain and muscle pain in the clinical development program. However a number of cases have been described in the post marketing data. The risk of arthralgia is described in the PI.

Saxagliptin CK

The sponsor has summarised the data from short and long term studies from the saxagliptin placebo controlled trials. This included 12 short term studies and 3 long term studies. The frequency of laboratory measurements ranged from 2-8 weeks in the short term studies and 6-14 weeks in the long term studies.

In the saxagliptin pools, there were 27 subjects with CK elevations >5X but ≤10X ULN, including 18 subjects who were treated with saxagliptin 5 mg and 9 subjects who received placebo. Two of the 18 subjects had laboratory values consistent with renal impairment that were temporally associated with the CK elevation. In 16 of the 27 subjects another reason for the raised CK was identified- this included other medications and exercise.

In the saxagliptin pools, there were 4 subjects (3 male and 1 female) with CK elevations, including 2 who were treated with saxagliptin 5 mg and 2 who received placebo. CK levels returned to normal or baseline values within an average of 23 days (range 7 to 56 days). All 4 subjects were asymptomatic at the time of the elevation and none required treatment. No subjects had any renal impairment associated with the CK elevation. There is a plausible alternative aetiology for the elevated CK for all 4 subjects: 1 was on a statin and a fibrate, 1 was taking other medications associated with increased CK (pioglitazone, cortisone, and alfuzosin), 1 reported physical exertion, and 1 subject had ureteric calculi.

A review of reports of rhabdomyolysis from the AstraZeneca Global Safety Database was conducted through 7 June 2016 for all clinical, spontaneous, and literature reports. This search identified 9 adverse event reports. All reports were either confounded by use of concomitant statin use, had an alternate explanation, or provided limited information.

A search of spontaneous reports of increased CK from the AstraZeneca Global Safety Database was conducted through 11 June 2016. This search identified 15 adverse event reports of increased CK. All 15 reports were confounded by medical history/risk factors and/or use of concomitant statin, had alternate explanation or provided limited information regarding the event.

DAPAGLIFLOZIN

A raised CK was seen in < 1% of patients in the dapagliflozin clinical development program. There was no imbalance between the number of cases with a raised CK in the dapagliflozin arm compared with the placebo arm. There were no symptomatic cases of rhabdomyolysis.

Risk management plan

The sponsor agreed to add 'DKA with atypical presentation' to the important identified risks.

Routine risk minimisation is proposed. Routine pharmacovigilance is proposed.

Risk-benefit analysis

Delegate's considerations

Raised CK

The sponsor has provided a detailed description of the cases of raised CK in the clinical development program of saxagliptin and dapagliflozin. The pattern of elevation of CK (that is, extremely high, transient, asymptomatic) is most consistent with a muscle related event rather than a drug induced myopathy. In most cases, there were other reasons for the elevation in CK. The AE were described as mild.

There was also an imbalance in the number of cases of raised CK in the saxagliptin clinical development program. There was no imbalance in the cases of raised CK in the dapagliflozin clinical development program. There have been no issues with raised CK in the post-market setting.

An elevated CK has been also described in diabetic patients. This is presumably due to the effect of changes in blood glucose, free fatty acid, ketone and other electrolytes on mitochondria and other components of muscle cells.

Risk-benefit balance

According to the EMA guidelines for FDC products:[14]

> *Applicants will be required to justify the particular combination of active substances proposed in the intended indication. For any individual FDC it is necessary to assess the potential advantages in the clinical situation against possible disadvantages, in order to determine whether the product meets the requirements of the standards and protocols with respect to efficacy and safety.*

The Delegate's concerns about the approval of this product from a regulatory perspective are:

- The sponsor has not justified the clinical need for the FDC Qtern as both saxagliptin and dapagliflozin are available as individual components. Both saxagliptin and dapagliflozin are second line therapies after metformin; thus, Qtern will be third line therapy.
- The advantages of taking two tablets instead of one for compliance have not been demonstrated. The patient population this FDC therapy will relevant for are patients with T2DM who have poor glycaemic control despite metformin. They are likely to have longstanding diabetes, have multiple co-morbidities, and be on a number of other medications (such as metformin, aspirin and a statin for cardiovascular protection, an ACE inhibitor for hypertension and/or renal protection at the least).

Benefits in efficacy of the FDC over individual components were marginal for the addition of the saxaglitpin component (see clinical trials).

Safety profile of this FDC is consistent with what would be expected from the safety profile of each individual component. In the clinical trials, the total number of AEs was similar with the use of saxagliptin + dapagliflozin + metformin than saxagliptin/metformin and dapagliflozin + metformin. This is somewhat unexpected as the AE profile for these two classes of drugs are different. In the clinical trials, the rate of discontinuations due to AE was higher in the saxaglitpin/dapagliflozin/metformin group.

There is no long term safety data (of more than 12 months) for the FDC of saxagliptin and dapagliflozin. In the long term safety study for saxagliptin (SAVOR), there was a signal for the risk of heart failure. The results of the long term cardiovascular study for dapagliflozin are not yet available.

From a clinical perspective, there is a need to individualise therapy in diabetes, and to simplify regimes where possible, particularly for the elderly. The use of any FDC limits the ability of physicians to titrate or stop an individual component. It may not be possible to determine which component of a FDC is responsible for the loss of efficacy or adverse events. These drugs have different roles in diabetes. DDP-IV inhibitors act by potentiating insulin secretion: they are more likely to be efficacious early in the course of diabetes and with smaller elevations in HbA1c. Dapagliflozin acts by increasing renal excretion of

[14] European Medicines Agency, "Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009.

glucose, and works better in patients with higher HbA1c. Thus, the characteristics of patients likely to respond to each individual drug are different.

The Delegate would recommend approval of this FDC if the sponsor could justify the clinical need for this FDC over the individual components which are on the ARTG. As this medicine would be the first registered agent for third line therapy on the ARTG, the PI and RMP needs to reflect this and include recommendations for monitoring of AE that may be associated with either or both drugs.

Indication

The proposed indication is more in line with the current indications for other FDC products in Australia and is acceptable. However, the EMA indication better describes the role of Qtern in therapy. The Delegate would recommend the EMA indication.

Summary of issues

Saxagliptin and dapagliflozin are both currently on the ARTG for the treatment of T2DM. Both agents are recommended as alternatives for second line therapy according to clinical guidelines.

Three clinical trials were submitted. One 24 week trial of saxagliptin/dapagliflozin added to patients inadequately controlled on metformin. In addition there was a 52 week study of saxagliptin added to patients with T2DM and poor glycaemic control on metformin and dapagliflozin; and a 52 week study of dapagliflozin added to patients with inadequate glycaemic control on saxagliptin and metformin.

The clinical trials showed a statistically significant improvement in HbA1c for the combination therapy – this seemed to be driven primarily by dapagliflozin. The additional improvement of saxagliptin over dapagliflozin was around 0.3% – which meets the regulatory requirement but is probably not clinically significant.

The Delegate's main concern about Qtern is that it includes two medicines that are both second line agents for T2DM. There is no advantage in this setting in reducing the number of tablets taken, as these patients are likely to be on a number of tablets. There is no significantly improved efficacy or safety with this combination due to the different mechanisms of action; in fact, the different medications are probably best for different diabetic phenotypes. The Delegate does not have concerns about using this combination of medicines as separate tablets, and would support the inclusion of the clinical trial information to relevant products, however having them as a FDC implies additional benefits which are not apparent.

Proposed action

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

Request for ACPM advice

- Do the benefits of this FDC outweigh the potential risks?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

AstraZeneca welcomes the opportunity to provide comments on the evaluation of the application proposing to register Qtern, a FDC containing saxagliptin and dapagliflozin, to improve glycaemic control in adults with T2DM for the following proposed indication:

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

AstraZeneca acknowledges the comments of the clinical evaluator that the dataset is in line with the accepted EU FDC guidelines[15] and the conclusion that the risk-benefit profile is acceptable to recommend registration of Qtern for the requested indication. AstraZeneca also acknowledges that the Delegate does not have concerns about using the combination of saxagliptin and dapagliflozin as separate tablets.

Proposed indication

AstraZeneca considers that the proposed indication noted above is appropriate for the target population. As discussed elsewhere in this response, AstraZeneca considers the saxagliptin/dapagliflozin FDC to be of significant clinical utility when metformin has not achieved a satisfactory level of glycosylated HbA1c reduction, should a physician consider the additional glycaemic control provided by the addition of the saxagliptin/dapagliflozin FDC desirable for an individual patient. The efficacy of the saxagliptin/dapagliflozin FDC is superior to that of either monocomponent without an adverse effect on safety. The modification proposed by the Delegate will remove a potential option to individualise therapy with a simplified regime. AstraZeneca, therefore, does not agree with the Delegate's proposal to amend the wording of the proposed indication.

AstraZeneca's proposed indication is in line with the indications for other oral medications recently approved by the TGA for treating T2DM, including FDCs for which indications have been written such that they are consistent yet simple. This approach for a simply worded indication is consistent with that proposed by TGA for the Forxiga submission (approved April 2014). The proposed PI provides details of the clinical use of the components of Qtern, saxagliptin and dapagliflozin, along with the pertinent safety information relevant to both components such that the prescriber is aware of instances when the FDC is not appropriate because of limitations posed by either dapagliflozin or saxagliptin. Therefore, the PI adequately describes the clinical settings where the combination can be used (including initial combination) and when considered in conjunction with the remainder of the PI, the proposed indication ensures safe and appropriate use of the FDC. It is also in line with the advice of the ACPM, provided previously as part of the consideration of the dapagliflozin/metformin (Xigduo XR) FDC, where advice was sought on the indication wording for FDC anti-diabetic products in general, and Xigduo XR specifically. In the meeting minutes, the ACPM advised that "in general, indications which are simpler and more consistent support improved management choices." The indication as proposed by AstraZeneca conforms with the advice previously provided by the ACPM and, even though alternate wording has been suggested, the Delegate has indicated that this approach is acceptable. Therefore, AstraZeneca does not consider that amendments to the proposed indication are required.

The clinical rationale for a FDC product with complementary mechanisms of action in the treatment of T2DM

T2DM is a progressive and widely prevalent disorder. There is a need for new treatment options and approaches to treatment. Therapy with saxagliptin and dapagliflozin added to

[15] European Medicines Agency, "Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009.

metformin as a FDC delivers significant reductions in HbA1c, with a low risk of hypoglycaemia. Each agent is efficacious when used alone, and the combination of the 2 agents, provides an even greater degree of glycaemic control, while maintaining a safety profile similar to that of its monocomponents. Use of the FDC enables combining the complementary mechanisms of action (MOAs) of saxagliptin and dapagliflozin, where there is the potential for effective HbA1c reduction (saxagliptin and dapagliflozin), reduction of body weight and blood pressure (dapagliflozin), glucose dependent insulin secretion (saxagliptin), and improvement in insulin sensitivity (dapagliflozin). Additionally, with the concomitant add-on approach, the saxagliptin/dapagliflozin FDC has the potential to achieve significant glycaemic control earlier, thereby providing a clinically important new option to other available oral and parenteral agents. There is growing evidence supporting early treatment intensification and the availability of a single FDC tablet will facilitate this approach to patient management by enabling the convenient addition of 2 complementary agents to supplement metformin.

As noted by the Delegate, patients with T2DM are likely to be receiving polypharmacy for a number of co-morbidities. Therefore, the availability of an FDC provides an opportunity to gain additional glycaemic control without adding further complexity to what may be an already complicated medication regimen. In patients with chronic conditions such as T2DM, FDCs should be considered for improving medication compliance by reducing pill burden, which can translate into better clinical outcomes.[16] AstraZeneca consider that an FDC containing saxagliptin and dapagliflozin will contribute to a more efficient management of T2DM by providing a treatment option with the potential to improve compliance.

Adherence to therapy is especially important in the management of chronic diseases such as T2DM, but the need for multiple anti-diabetes medications to achieve and then sustain adequate HbA1c control often leads to poor adherence. Recent reviews indicate that the incidence of non-adherence in patients with T2DM ranges from 10% to 30%.[17] Poor adherence leads to inadequate glycaemic control and subsequently increased risk of associated complications. In patients with T2DM, denial of the disease and difficulties in making the recommended lifestyle changes are common. The importance of good compliance in the T2DM patient population should not be underestimated. With an FDC product, there are the potential advantages of improved patient compliance, treatment satisfaction, and lower overall cost of treatment.[18]

The efficacy of the saxagliptin/dapagliflozin FDC is superior to that of either monocomponent with a safety profile consistent with that of its monocomponents. HbA1c was reduced by 1.47% and 41.4% of subjects achieved glycaemic goal, which is a 2-fold improvement compared with the monocomponents, with no increased risk of hyperglycaemic events. As such, the combination of saxagliptin and dapagliflozin, with their complementary MOAs, offers an improved benefit over either monocomponent with a similar risk profile compared with either monocomponent across the entire target population.

[16] Bangalore S, et al. Compliance and fixed-dose combination therapy. *Curr Hypertens Rep.* 9: 184-9 (2007).
[17] Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 27: 1218-24 (2004); Schernthaner G. Fixed-dose combination therapies in the management of hyperglycaemia in Type 2 diabetes: an opportunity to improve adherence and patient care. *Diabet Med.* 27: 739-43 (2010); Skaer TL, et al. Effect of value-added utilities on prescription refill compliance and Medicaid health care expenditures--a study of patients with non-insulin-dependent diabetes mellitus. *J Clin Pharm Ther.* 18: 295-9 (1993);
[18] Bell DS. Combine and conquer: advantages and disadvantages of fixed-dose combination therapy. *Diabetes Obes Metab.* 15: 291-300 (2013); Hutchins V, et al. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. *Curr Med Res Opin.* 27: 1157-68 (2011).

The benefits of early treatment intensification in the treatment of T2DM

Today, T2DM is a leading cause of cardiovascular disorders, blindness, end stage renal failure, amputations, and hospitalisations,[19] which has been attributed to glucotoxicity and its long-term microvascular and macrovascular consequences. The majority of diabetes associated microvascular complications are proportional to the degree and duration of hyperglycaemia. New data from the follow-up studies of the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study Group (UKPDS) emphasise the role of early glycaemic control in preventing subsequent complications. The concept of a "metabolic memory" (DCCT Research Group) or "legacy effect" (UKPDS Group) was created to stress that abnormal function in some tissues persists even after a patient has reached a targeted glycaemic response.[20] Further, T2DM results in histopathological changes in multiple organs (for example, basal membrane thickening in the renal tubuli), which may be difficult to reverse. In newly diagnosed patients with T2DM, a 1-year delay in achieving good glucose control has been associated with an increased risk of macrovascular complications and developing myocardial infarction, heart failure, stroke and composite cardiovascular events.[21]

Early treatment intensification may reduce both microvascular and macrovascular complications, and this highlights the importance of achieving and maintaining guideline recommended glycaemic and metabolic targets. Thus, the traditional stepwise approach to diabetes care is no longer appropriate for all patients, provided that the benefits of drug therapy are not outweighed by safety concerns, such as an increased risk of hypoglycaemia. The saxagliptin/dapagliflozin FDC is ideal in this context, because it confers a high degree of clinical efficacy, without the risk of hypoglycaemia, and with a safety profile that is consistent with its monocomponents. These glycaemic benefits are accompanied by clinically relevant reductions in blood pressure and body weight and the agents can be administered as a convenient, single pill with a potential increase in patient compliance.

The therapeutic advantage of initiating concomitant treatment with saxagliptin and dapagliflozin

Effects on HbA1c

The concomitant initiation of saxagliptin and dapagliflozin in subjects inadequately controlled on metformin alone led to a greater mean reduction in HbA1c over the 24-week treatment period (-1.47%) compared with adding saxagliptin alone and dapagliflozin alone to metformin (-0.88% and -1.20%, respectively). Additionally, the saxagliptin/dapagliflozin plus metformin treatment group showed a significant difference in adjusted HbA1c mean change from baseline versus saxagliptin plus metformin (-0.59%, $p<0.0001$) and versus dapagliflozin plus metformin (-0.27%, $p = 0.0166$), demonstrating that saxagliptin and dapagliflozin each contribute significantly to the efficacy of the combination.

For almost all diabetes medications, the treatment effect is greatest in patients with higher baseline HbA1c values and it progressively lessens in patients with lower baseline HbA1c values. In practice, this means that monotherapy is often sufficient to lower HbA1c to <8% or <7.5%, but additional therapies are needed to incrementally reduce HbA1c below the treatment goal of HbA1c <7%. Therefore, given the increased difficulty of HbA1c improvement in this range and the importance of meeting glycaemic targets, it is the

[19] Inzucchi SE. Clinical practice. Diagnosis of diabetes. *N Engl J Med.* 367: 542-50 (2012).
[20] Ceriello A. Hypothesis: the "metabolic memory", the new challenge of diabetes. *Diabetes Res Clin Pract.* 86 Suppl 1: S2-6 (2009).
[21] Paul SK, et al. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. *Cardiovasc Diabetol.* 14: 100 (2015).

totality of the glycaemic effect achieved by the FDC that is of clinical relevance and importance.

The determination of the contribution of each individual component of the FDC is challenging. For both saxagliptin and dapagliflozin, the change from baseline in HbA1c after 24 weeks of treatment is positively related to the baseline HbA1c level. In the concomitant add-on setting, where each component is significantly reducing HbA1c (and hence the effect of the other component), it would seem reasonable to assume that the efficacy contribution of each component is reduced from that observed when used as a single add-on component. A simple arithmetic sum of the reductions achieved with each monocomponent is -2.08%, which differs from the -1.47% reduction seen with concomitant saxagiptin and dapaglifozin, and represents a difference of approximately 30%. This is consistent with what has been seen with currently available FDCs for treating T2DM.[22] One way to estimate the contributions of the monocomponents is to simply assume the same 30% reduction of effect for each monocomponent. Under that assumption, the estimates of the contributions of each of the monocomponents to the concomitant add-on effect would be -0.85% for dapagliflozin and -0.62% for saxagliptin (which sum to -1.47%). While these values are based on an assumption (and, in particular, treat placebo effects as negligible), they illustrate that the contribution of each component to the mean reduction of -1.47% achieved with concomitant saxagliptin and dapagliflozin are likely considerably higher than the -0.27% and -0.59% differences versus the monocomponents that are often labelled as monocomponent contributions.

Achieving therapeutic glycaemic goal

The proportion of subjects who achieved therapeutic glycaemic goal (that is, HbA1c <7.0%) after initiating the concomitant treatment with saxagliptin and dapagliflozin was approximately 2-fold higher (41.4%) compared with saxagliptin alone (18.3%) and dapagliflozin alone (22.2%). AstraZeneca considers these differences to be clinically meaningful apart from the absolute reduction in HbA1c.

Effects on body weight and blood pressure

In Study CV181169, the concomitant initiation of saxagliptin and dapagliflozin led to a decrease in mean body weight (-2.05 kg). The decrease in body weight is attributed to the dapagliflozin component and is consistent with the dapagliflozin MOA. Also, as consistently observe across the dapagliflozin development programme, there was a modest decrease in blood pressure observed in the combined treatment group.

Effects on renal function

A trend towards decreased albumin/creatinine ratio (ACR) in the saxagliptin/dapagliflozin arm was found in Study CV181169, but due to a relatively small sample, a definitive effect was not established. Based on the known effects of saxagliptin and dapagliflozin, the contribution of each component may stem from different and potentially complementary mechanisms that are largely independent of the HbA1c lowering effects of both saxagliptin (SAVOR study)[23] and dapagliflozin.[24] The potentially complementary effect of saxagliptin and dapagliflozin on ACR is being assessed in ongoing studies.

[22] Rosenstock J, et al. Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. *Diabetes Care* 39: 2026-35 (2016).
[23] Udell JA, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. *Diabetes Care* 38: 696-705 (2015).
[24] Heerspink HJ, et al. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation* 134: 752-72 (2016).

Similar to other dipeptidyl peptidase 4 inhibitors, saxagliptin has beneficial renal effects as demonstrated by reductions in ACR. The beneficial effects of saxagliptin on ACR observed in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus clinical study (SAVOR) were obtained on top of the renin-angiotensinaldosterone system inhibition.[25]

Safety and tolerability

The clinical development programme for the saxagliptin/dapagliflozin FDC comprised 3 Phase III, randomised, double blind, active/placebo controlled, parallel group, multicentre clinical studies (CV181168, MB102129 and CV181169), which enrolled 1169 subjects who were treated for up to 52 weeks. Data from these studies were pooled to evaluate the safety and efficacy of combining saxagliptin 5 mg and dapagliflozin 10 mg in adult subjects with T2DM who had inadequate glycaemic control on metformin.

The safety profile for the combined use of saxagliptin and dapagliflozin in the pooled studies indicated that treatment was well tolerated. The incidence of hypoglycaemia reported with the combined use of saxagliptin and dapagliflozin was low (1.4%, excluding data after rescue). No major episodes of hypoglycaemia were reported, and none of the subjects discontinued their study treatment because of hypoglycaemia.

Co-administration of saxagliptin and dapagliflozin was not associated with additive adverse effects as the incidence and type of AEs reported when saxagliptin and dapagliflozin were concomitantly added to metformin were similar to when the individual agents were added to metformin.

Individually, both saxagliptin and dapagliflozin continue to demonstrate favourable and well characterised safety profiles. Approximately 20,800 subjects and at least 18,000 subjects have been exposed to saxagliptin and dapagliflozin, respectively, in their clinical development programmes. Additionally, as of the fourth quarter of 2015 the total cumulative worldwide marketing exposure has been estimated at approximately 2.5 million patients-years for saxagliptin and 687,032 patient-years for dapagliflozin. Extensive clinical study and postmarketing data with each of the monocomponents continue to support the long term safety profile of the saxagliptin/dapagliflozin FDC.

Specific adverse events related to the safety profile of the individual monocomponents are clearly outlined in the respective Adverse Effects sections of the Australian PIs. In addition, the Contraindications and Precautions sections of each PI inform prescribers about important potential risks, patient populations that might be susceptible to certain effects of the drug, and instruct about correct use of each monocomponent. The proposed PI for Qtern also refers prescribers to the approved PIs for the monocomponents for detailed information about adverse effects that may be associated with saxagliptin or dapagliflozin. This enables prescribers to recognise events related to either monocomponent, as well as the potential risks with the use of each monocomponent.

Summary of clinical benefits

The concomitant approach to treatment with saxagliptin/dapagliflozin added to metformin has the potential to bring patients to their glycaemic goals more quickly, thus reducing or delaying complications of T2DM in a difficult-to-treat population. The saxagliptin/dapagliflozin FDC is a novel oral regimen with the potential to achieve earlier and significant glycaemic control, with a low rate of hypoglycaemia, modest weight loss and reduction in BP, and a safety profile that is consistent with that seen for the monocomponents.

[25] Udell JA, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. *Diabetes Care* 38: 696-705 (2015).

Increased creatine kinase

As discussed by the Delegate, AstraZeneca conducted a thorough review of marked CK elevations observed in the saxagliptin plus dapagliflozin development programme. The results of extensive analyses indicate that transient asymptomatic CK elevations occur in this patient population and do not suggest a possible causal relationship of CK elevations of >5X the upper limit of normal with saxagliptin plus dapagliflozin. Consequently, AstraZeneca considers that no changes to the safety information are required.

Amputations

AstraZeneca has reviewed data from completed clinical trials and post-marketing data regarding the occurrence of amputation. Data from clinical trials do not indicate a higher incidence of non-traumatic lower-limb amputations in patients treated with dapagliflozin compared with control and no signal from case reports from post-marketed reports has been found.

Thus, no signals have been identified for the occurrence of amputation in clinical studies and in post-marketing data for dapagliflozin. This was communicated to TGA.

The conclusion in the previous response was:

> *In summary, based on data from completed studies and post-marketing experience, no change to the dapagliflozin PI or RMP regarding amputation is warranted.*

Based on the available data to June 2016, this conclusion remains unchanged.

Health Authority reviews were initiated following an increase in amputations, mostly affecting toes, observed in the ongoing canagliflozin clinical trial, CANVAS. The occurrence of amputation during treatment with dapagliflozin is currently under review by the FDA and EMA, and neither agency has recommended an update of the dapagliflozin label based on the available data, at this stage.[26] There are ongoing discussions regarding a potential mechanism; however, a potential mechanism and potential risk factors have, as of the date of this document, not been established.

It should be noted that the approved PIs for other SGLT2 inhibitors do not currently include a statement regarding the potential risk of amputations. Therefore, the inclusion of a precaution describing amputations associated with another drug in this class without consistency across the PIs for all SGLT2 inhibitors would not seem appropriate. Thus, it is the opinion of AstraZeneca that it is not appropriate to include any statements related to the topic of amputation in the PI.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Qtern tablets blister pack containing 5 mg saxagliptin/10 mg dapagliflozin to have an overall positive benefit-risk profile for the Delegate's amended indication:

> *Qtern is indicated in adults with type 2 diabetes to improve glycaemic control when metformin and one of the components of Qtern do not provide adequate glycaemic control or when already being treated with the free comination of dapagliflozin and saxagliptin.*

In making this recommendation, the ACPM:

- Noted that this is the first FDC without metformin for the treatment of T2DM. Both saxagliptin and dapagliflozin are adjuncts to treatment or second line alternatives.

[26] This was June 2016.

- Accepted the role of both drugs in diabetes management but was of the opinion that in terms of efficacy dapagliflozin outweighs saxagliptin. The committee accepts that the risk-benefit balance is acceptable and it is approvable as a 3rd line agent.
- Was satisfied with the drug product itself and that neither active ingredient had any major relevant activity on the metabolism of the other ingredient.
- Was satisfied with issues related to CK elevations. There was a small number (n = 7) of subjects in clinical trials with elevated CK (> 5 x ULN) and all subjects had confounding risk factors.
- Accepted that a FDC may increase compliance in some patients, there may be a small benefit in terms of treatment satisfaction and it may lower overall cost of treatment.
- Was considered unsatisfactory on the argument of moving from metformin therapy to a treatment regime containing a FDC with two new drugs (neither previously trialled). Whilst the FDC has a favourable risk-benefit balance, current practice follows the stepwise approach to augmentation of diabetes treatment (that is both components of the FDC should be trialled in sequence, rather than both initiated in parallel) and the ACPM stresses the importance of physician-patient relationships in diabetes management. The ACPM therefore favoured an indication and position as of that or similar to that of EMA.

Proposed conditions of registration

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

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Caution on the risk of possible inadvertent toxicity in renal impairment as the FDC cannot be titrated.
- Caution on the safety of use in patients > 75 years without evidence of patient renal function.
- Caution on use in patients with an eGFR < 60 due to reduced efficacy of SGLT-2 inhibitors, and the need for regular renal monitoring especially on drug initiation.
- Inclusion that there is a possible risk of amputation that may be a drug-class event associated with the SGLT2 inhibitors. The importance of regular foot examination should be included in the PI.

Specific advice

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

- *Do the benefits of this FDC outweigh the potential risks?*

From a safety and efficacy view point, both active drug components of the FDC have a place in the treatment of T2DM and there are no issues with the two components being given together in a single drug product. The ACPM however strongly advised that in accordance with the diabetes treatment guidelines in clinical use both in Australia and overseas, patients should not move from metformin to a combination of metformin and the proposed FDC, but similar to the European indication, one of the active drugs in the FDC should be trialled first before adding the other in a sequential fashion.

Post ACPM considerations

Following the ACPM in August 2016, there were further discussions between the sponsor and Delegate. These are included below.

Indications

Delegate's comments to the sponsor

The Delegate has considered the committee's advice and the sponsor's pre ACPM response and proposes to approve the submission with the following amended indication:

> *Qtern is indicated in adults with type 2 diabetes to improve glycaemic control when metformin and one of the components of Qtern do not provide adequate glycaemic control or when already being treated with the free combination of dapagliflozin and saxagliptin.*

Changes to the PI and RMP as described below are required. To facilitate the finalisation of this submission, the Delegate requests that the sponsor provide updated PI and CMI documents incorporating the following amendments. The recommendations below refer to the annotated PI provided in the sponsor's pre ACPM response and should be used as the basis for these changes.

PI

Indications:

> *Qtern is indicated in adults with type 2 diabetes*
>
> - *to improve glycaemic control when metformin and one of the components of Qtern do not provide adequate glycaemic control*
> - *when already being treated with the free combination of dapagliflozin and saxagliptin.*

Sponsor response: September 2016

Following receipt of the ACPM resolution and the Delegate's request for amendments to the proposed indication for Qtern, the sponsor wishes to take this opportunity to reiterate its position that the indication proposed by the sponsor as shown below and the potential use of the FDC as an option to follow on from metformin therapy is appropriate.

> *Qtern is indicated in adults with type 2 diabetes in combination with metformin to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.*

The choice, order and combination of medications used to manage a patient's glycaemic levels should be based on evidence of efficacy, risk of side effects and patient choice/capacity. While the sponsor recognises that a stepwise approach to therapy is recommended by the Australian guidelines, the guidelines also note glycaemic management is becoming more complex with an increasing range of medicines available and a simple stepwise approach does not always neatly match individualised patient needs. Further, the decision to register a medicine or new indication should be based on the evidence of safety, efficacy and quality, which may not necessarily be consistent with existing treatment algorithms or current clinical practice. A reliance on existing guidelines or treatment practice on that basis would inherently preclude the registration of new medicines or novel indications, which by their very nature may not feature in treatment guidelines at the time of their initial registration.

The use of the FDC has been shown to have a favourable risk-benefit balance, when used in the dual add-on setting as a follow on treatment with metformin when additional glycaemic control is required. The concomitant initiation of saxagliptin and dapagliflozin

in subjects inadequately controlled on metformin alone was well tolerated and led to a greater mean reduction in HbA1c over the 24 week treatment period with a low incidence of hypoglycaemia. Almost twice as many patients treated with the FDC achieved HbA1C <7% compared with monocomponents at Week 24. In addition to the potential for effective HbA1c reduction, each component can provide therapeutic advantages to the patient based on their mechanism of action such as the reduction of body weight and blood pressure along with improvement in insulin sensitivity associated with dapagliflozin and the glucose dependent insulin secretion seen with saxagliptin. Co-administration of saxagliptin and dapagliflozin was not associated with additive adverse effects as the incidence and type of AEs reported when saxagliptin and dapagliflozin were consistent when used concomitantly as dual add-on therapy or added in a stepwise manner. As such, the combination of saxagliptin and dapagliflozin, with their complementary mechanisms of action, offers an improved benefit over either monocomponent with a similar risk profile compared with either monocomponent across the entire target population.

Applying the principles of patient centred care may mean that choices made by algorithm or guideline recommendations are not always appropriate. As stressed by the ACPM in the resolution, physician-patient relationships in successful diabetes management are of paramount importance, and as such the sponsor considers the modification proposed by the ACPM will remove a potential option to individualise therapy when a traditional stepwise approach may not be the better option following a holistic consideration of the patient's needs and preferences.

The concomitant approach to treatment with the saxagliptin/dapagliflozin FDC added to metformin has the potential to bring patients to their glycaemic goals more quickly, thus reducing or delaying complications of T2DM in a difficult-to-treat population. The saxagliptin/dapagliflozin FDC is a novel oral regimen with the potential to achieve significant and durable glycaemic control earlier in comparison with either sequential approach or monocomponent use, with a low rate of hypoglycaemia, modest weight loss and reduction in blood pressure, and a safety profile that is consistent with that seen for the monocomponents. Therefore, the sponsor considers the indication should not be modified as recommended by the ACPM as this will remove an option for individualisation of patient therapy with a treatment demonstrated to be both safe and effective.

Additionally, the sponsor considers, should the Delegate wish to not approve the use of the FDC as a dual add-on therapy following metformin, the indication wording proposed above to be preferable to that recommended by the ACPM. The sponsor's proposed indication is in line with the indications for other oral medications recently approved by the TGA for treating T2DM, including FDCs for which indications have been written such that they are consistent yet simple. The indication as proposed by the sponsor conforms with previous guidance provided by the TGA for other medicines used in the management of diabetes and the advice provided on a previous occasion by the ACPM that "in general, indications which are simpler and more consistent support improved management choices". The proposed PI provides details of the clinical use of the components of Qtern, saxagliptin and dapagliflozin, along with the pertinent safety information relevant to both components such that the prescriber is aware of instances when the FDC is not appropriate because of limitations posed by either dapagliflozin or saxagliptin. Therefore, the PI adequately describes the clinical settings where the combination can be used and when considered in conjunction with the remainder of the PI, the proposed indication ensures safe and appropriate use of the FDC.

Amputations

TGA requested changes to PI and RMP

PI

Precautions:

- *Feet examinations:*

  An increased risk of amputations has been identified during a clinical trial of another SGLT-2 inhibitor. There has been no increased risk identified with dapagliflozin, however patients and practitioners are reminded of the need for regular foot examinations in patients with diabetes.

RMP

Based on the ACPM advice, the following safety concerns should be added as important identified risks to revised versions of the RMP and ASA:

- *amputation*

The revised ASA should also include the pharmacovigilance and risk minimisation activities that will be undertaken to address these safety concerns. Routine pharmacovigilance and risk minimisation (in the form of precautions in the PI and information in the CMI) are considered to be adequate activities for these safety concerns.

A revised RMP and ASA should be submitted to the TGA for consideration by the RMP Evaluator who will negotiate the final content of the RMP and ASA. Once agreed with the TGA, the revised versions of the RMP and ASA will be implemented as a condition of registration.

Sponsor response: September 2016

The sponsor has reviewed data from completed clinical trials and postmarketing data regarding the occurrence of amputation. Data from clinical trials do not indicate a higher incidence of non-traumatic lower limb amputations in patients treated with dapagliflozin compared with control and no signal from case reports from postmarketed reports has been found.

There are 30 completed dapagliflozin studies of 12 or more weeks duration (including saxagliptin/dapagliflozin studies). Surgery data like amputations are considered as a procedure and hence are not generally recorded as adverse events. In clinical studies, the investigators are instructed to report the underlying diagnosis for the procedure and not the procedure itself. Therefore, to identify potential amputation events a free text search of "amput" was conducted for the 30 completed studies. Both AE and SAE case report form data for all individual study databases and all clinical study reports were searched. In these studies, there were 19 non-traumatic lower limb amputations identified: 8 patients with 12 events in 9195 patients (8058.6 patient-years exposure) on dapagliflozin and 7 patients with 7 events in 4629 patients (4177.1 patient-years exposure) on control.

These data do not indicate a higher incidence of non-traumatic lower limb amputations in patients treated with dapagliflozin compared to control.

The sponsor has also conducted analysis of AEs thot could potentially lead to amputation as listed below:

> *Skin ulcer, Peripheral ischemia, Peripheral vascular disorder, Gangrene, Cellulitis, Wound, Peripheral arterial occlusive disease, Intermittent claudication, Diabetic foot, Diabetic foot infection, Diabetic neuropathic ulcer, Diabetic ulcer, Infected skin ulcer, Neuropathic ulcer, Skin erosion and Skin ulcer haemorrhage*

The review of these events, which could potentially lead to amputations, did not indicate an imbalance in events between dapagliflozin and placebo/comparators in these trials.

The sponsor also analysed events in the placebo controlled pools with short term (ST) and ST + long term (LT) treatment periods (placebo controlled pools) from the 30 month safety update (previously submitted and approved for inclusion in the Forxiga PI). The ST + LT placebo controlled pool included 9 placebo controlled clinical studies that included 2026 subjects receiving dapagliflozin 10 mg and 1956 subjects receiving placebo. The incidences of events were similar: there were 106 (5.2%) and 109 (5.6%) subjects with events in the dapagliflozin 10 mg and placebo groups, respectively. The ST placebo controlled pool included 13 placebo controlled clinical studies that included 2360 subjects receiving dapagliflozin 10 mg and 2295 subjects receiving placebo. There were 54 (2.3%) and 58 (2.5%) subjects with events in the dapagliflozin 10 mg and placebo groups, respectively.

For the postmarketing findings on non-traumatic lower limb amputations, the sponsor's global safety database was searched for all spontaneous AE reports up to April 2016 in association with the use of dapagliflozin or the dapagliflozin/metformin FDC. As surgery data like amputations are considered as a procedure and hence are not generally recorded as AEs, a free text search of the narratives for all dapagliflozin and dapagliflozin/metformin case reports in the database was performed using the search criteria "amput". The results of this cumulative free text search were reviewed and a total of 2 cases were identified which reported amputations during treatment with dapagliflozin or dapagliflozin/metformin in the postmarketing setting.

DECLARE TIMI-58 study is an ongoing large cardiovascular outcome study with 17,276 randomised subjects (dapagliflozin or placebo randomised 1:1) in subjects with T2DM who have inadequate glycaemic control and either a history of a prior CV event or 2 or more risk factors for a CV event. Last patient was randomised 30 June 2015. Following a request from the EU PRAC and ad hoc review of DECLARE data was undertaken looking at amputations by the independent Data Monitoring Committee. Following the review of reported events the DMC recommended DECLARE to continue as per the current protocol in June 2016.

Health Authority reviews were initiated following an increase in amputations, mostly affecting toes, observed in the ongoing canagliflozin clinical trial, CANVAS. The occurrence of amputation during treatment with dapagliflozin is currently under review by the US FDA and EMA, and neither agency has recommended an update of the dapagliflozin label based on the available data, at this stage. There are ongoing discussions regarding a potential mechanism; however, a potential mechanism and potential risk factors have, as of the date of this document, not been established.

Currently available data do not enable the identification of a likely mechanism by which SGLT2 inhibition, directly or indirectly, could lead to an increased risk of amputation. Due to the localization of the SGLT2 receptor almost exclusively to the kidney, it is unlikely that SGLT2 inhibitors have a direct effect on risk factors affecting amputation rate, such as neuropathy, PAD, infection, and wound healing.

Empagliflozin and dapagliflozin are structurally very similar, with some differences compared with canagliflozin. There are intra-class differences between the drugs with respect to SGLT1 affinity and dose-response relationship. In the EMPA-REG study for empagliflozin, which included a similar population to that of the CANVAS study, the frequencies of lower limb amputations were similar between the empagliflozin and placebo groups (empagliflozin and placebo) and there was no signal of an increased amputation risk, although data on amputation were not systematically collected. In completed dapagliflozin studies, the frequencies of AEs that could potentially lead to amputations were generally similar in the completed dapagliflozin studies, and review of

DECLARE TIMI-58 data has not indicated an increased frequency of amputations or an imbalance between treatment groups of the magnitude seen in the CANVAS study.

It is the sponsor's position that the currently available evidence does not indicate that a potential increased risk of amputations is a SGLT2 inhibitor class effect. No imbalance in amputation events has been identified for dapagliflozin. Therefore, no additional pharmacovigilance and risk minimisation measures are proposed at present.

However to enable data on amputation to be systematically collected in clinical studies, the sponsor will introduce a dedicated eCRF module for collection of information on all amputations. The eCRF module will include detailed information-gathering regarding underlying conditions. With this information, the risk of having an amputation as well as the risk of progressive disease and future amputations could be analysed.

The sponsor plans to introduce such a dedicated eCRF module in future, larger studies of greater than three months duration, with the goal of collecting amputation events in sponsor-sponsored clinical studies regardless of aetiology.

The eCRF module will also be implemented in the ongoing DECLARE TIMI-58 study. The DECLARE TIMI-58 study is event driven and has an expected median follow-up of 4.5 years. Enrolment is completed and 17,276 subjects have been randomised. The sponsor estimates that 50% of the planned 1390 MACE events have been adjudicated and confirmed in the fourth quarter of 2016; however, the sponsor intends for the amputation eCRF page to be filled in retrospectively for events that have previously been reported or identified through the sponsor's and TIMI's extended search.

In upcoming PSUR/PBRERs for dapagliflozin, data relevant to amputation events will be analysed and presented. A full assessment of lower limb amputations in DECLARE TIMI-58 study will be included in the CSR and PSUR/PBRER when the study has been finalised and unblinded.

Amputation and related terms are continuously monitored as part of the sponsor's pharmacovigilance program, in which safety signals from various sources are identified and evaluated. To date, no safety signal has been raised. Based on this cumulative review of postmarketing reports, it is the sponsor's view that there is no evidence from postmarketing use that dapagliflozin or the dapagliflozin/metformin FDC is associated with an increased risk of amputation.

As no increased risk of amputations has been identified for dapagliflozin, it is not possible to establish whether specific patient populations would be at a higher differential risk, including subgroups which would already be at an increased risk of amputations due to their baseline disease. Additionally, no mechanism has been identified by which SGLT2 inhibition could theoretically lead to an increased risk of amputations. Therefore, it is the sponsor's position that no meaningful wording can be proposed for the product information.

As there is significant uncertainty in relation to the potential of an increased risk of amputations in association with SGLT2 use and the linkage between the EU risk management activities and the Australian submission, the sponsor respectfully suggests it would be useful to await the outcome of the in depth review of the SGLT2 class currently being undertaken by the EMA Pharmacovigilance Risk Assessment Committee (PRAC). Therefore, the sponsor proposes a commitment to communicate the outcome of the PRAC review when available to TGA in order to have a consistent approach, in lieu of the immediate changes to the PI and RMP.

Delegate's comments to the sponsor: September 2016

The Delegate accepts the sponsor's response to the ACPM's advice in relation to the indications, and therefore approves the following indication for Qtern:

> *Qtern is indicated in adults with type 2 diabetes in combination with metformin to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.*

The Delegate has read the sponsor's response in relation to the potential risk of amputation with SGLT-2 inhibitors. Although it was been proposed that this risk may be a class effect, there is no evidence to support this concern as amputations have not been associated with any safety signals with either dapagliflozin or empagliflozin. The Delegate therefore approves of the proposal not to include the potential risk of amputations in the PI at this stage. However, should the EMA's PRAC or the US FDA consider the risk of amputations is a class effect, TGA will require the sponsor update the PI of the dapagliflozin products accordingly.

In relation to the RMP, it is apparent that the sponsor has initiated a number of strategies to improve the detection of cases of amputations and risk factors associated with this through their eCRF module which will be implemented in the ongoing DECLARE-TIWI-58 study and upcoming PSUR/PBRERs. The Delegate would support the addition of amputation as a potential risk in the ASA; however, the decision in relation to the RMP is the responsibility of TGA's Post Market Surveillance Branch.

In relation to the PIs, the Delegate has attached the PIs and CMIs with some changes and comments. Most of the changes are to increase the readability of the document, clarify use in renal impairment, and clarify dosing instructions.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Qtern 5/10 saxagliptin (as hydrochloride)/dapagliflozin (as propanediol monohydrate) 5 mg/10 mg film-coated tablet blister pack for the following indication:

> *Qtern 5/10 is indicated as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.*

Specific conditions of registration applying to these goods

- The Qtern saxagliptin hydrochloride/dapagliflozin propanediol monohydrate EU RMP, version 2.2, dated 4 July 2016 (data lock point, 5 February 2016) with ASA, version 3, dated 6 October 2016, and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Qtern at the time this AusPAR was published is at Attachment 1. For the most recent PI, 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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